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SYNTHESIS AND PHARMACOLOGY OF SOME ACETYLCHOLINE ANALOGS AND NEUROMUSCULAR BLOCKING AGENTS

BY

IH CHU

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

SPRING, 1973

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "Synthesis and Pharmacology of Some Acetylcholine Analogs and Neuromuscular Blocking Agents" submitted by Ih Chu in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

Geometrically isomeric pairs of 2-, 3- and 4-methyl-1-dimethylaminomethylcyclohexyl acetate methiodides (14b, 14c and 14d respectively), the corresponding desmethyl derivative (14a), acetyl-β,β-dimethylcholine iodide (16), (1-N,N-dimethylaminocyclohexyl)-methyl acetate methiodide (21), cis- and trans-1-acetoxy-2-dimethylaminoindan methiodide (26 and 30), and the diphenyl acetates (38 and 40) have been prepared and evaluated for muscarinic and nicotinic activity on the guinea pig ileum or frog rectus muscle. The configuration of cis,trans pairs and certain conformational features were elucidated from spectroscopic (IR and PMR) data. Only acetyl-β,β-dimethylcholine iodide (16), and (1-N,N-dimethylaminocyclohexyl)-methyl acetate methiodide (21) showed any muscarinic activity on the guinea pig ileum. None of the compounds possessed any antimuscarinic, nicotinic, or antinicotinic properties on this preparation in the doses studied. On the frog rectus muscle no compound possessed spasmogenic activity but all compounds were approximately 0.05 times as active as gallamine in antagonizing responses to ACh. The effect of (+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide has also been studied and found to be of an indirect nature on the guinea pig ileum. The muscarinic properties of these compounds are discussed in terms of their probable conformations and evidence that ACh agonists adopt antiperiplanar (or near antiperiplanar) $^{+}N/O$ conformations at muscarinic receptors.

ABSTRACT

6- and 7-Dimethylamino-1-tetralone hydrazone methiodide (78 and 88), 5-dimethylamino-1-tetralone hydrazone methyl tosylate (98), 4-, 5- and 6-dimethylamino-1-indanone hydrazone methiodide (144, 135 and 141 respectively), and the N,N-dimethylhydrazones (106 and 107) were synthesized and evaluated for neuromuscular blocking activity on the frog rectus abdominis muscle and the cat sciatic nerve tibialis muscle. All compounds demonstrated, in varying degree, some activity on the frog rectus muscle. Only 6-dimethylamino-1-tetralone hydrazone methiodide, 5-, and 6-dimethylamino-1-indanone hydrazone methiodide showed activity comparable to suxamethonium on the cat sciatic tibialis muscle. The Structure-Activity Relationship of these compounds is discussed.

ACKNOWLEDGEMENTS

The author wishes to extend his most sincere thanks to Drs. D. F. Biggs, A. F. Casy and R. T. Coutts for their supervision and encouragement throughout the course of this work.

FOREWORD

This thesis is concerned with two aspects of the chemical transmission of nerve impulses that are mediated by acetylcholine (ACh) and may be conveniently divided into two parts. In Part I a study of the influence of stereochemistry upon the muscarinic activity of acetylcholine is made whilst in Part II attention is focussed on a series of aminotetralone derivatives and analogs which antagonize the nicotinic effect of acetylcholine at the neuromuscular junction.

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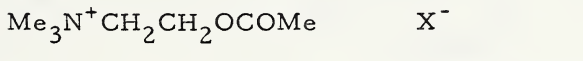
PART I

SYNTHESIS AND PHARMACOLOGY OF SOME ACETYLCHOLINE ANALOGS

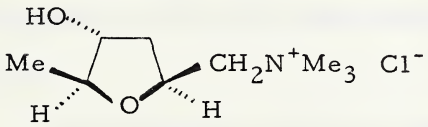
INTRODUCTION

One of the functions of acetylcholine (ACh, 1) is the trans-



1

mission of nerve impulses between neurons, between neuron and muscle, and between neuron and secretory cell within the parasympathetic nervous system (Nachmansohn, 1959). Some of its functions in this respect are simulated by (+)-muscarine (2) and others by nicotine (3). The two types of action suggest that there



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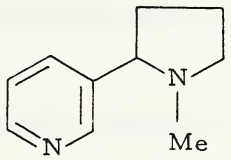
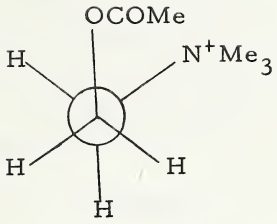
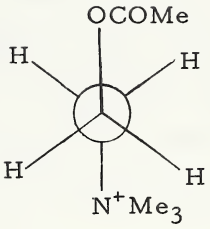


3

are at least two types of ACh receptors, and may also suggest the existence of different conformational isomers of ACh which may interact with these receptors (Portoghese, 1970; Martin-Smith et al., 1967). It may be proposed for example that the ACh molecule in the gauche form (1a) interacts with muscarinic receptors but not nicotinic receptors, the reverse being true for the trans conformer (1b).



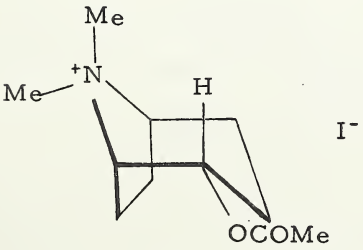
1a gauche



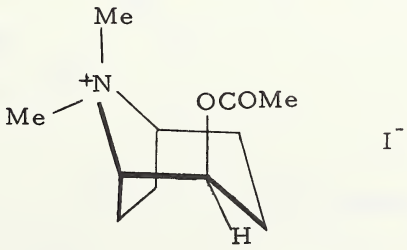
1b trans

Experimental approaches to gaining evidence about the role of conformational isomerism in the pharmacological actions of ACh include 1) the synthesis and pharmacological evaluation of structurally rigid analogs which reproduce in varying degree, gauche and trans conformers of ACh and 2) investigation of the conformational preferences of ACh under physiological conditions by spectroscopic methods.

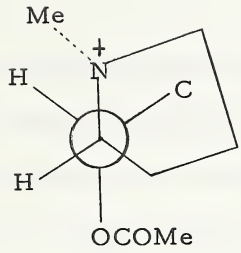
Recently many conformationally restrained analogs of ACh have been made and tested pharmacologically in order to determine the possible conformations of ACh which are responsible for muscarinic and nicotinic effects. Archer et al. (1962) first prepared both diastereomers of 2-tropanyl acetate methiodide (4a and 4b), and found that 4a favored muscarinic action whereas 4b was primarily



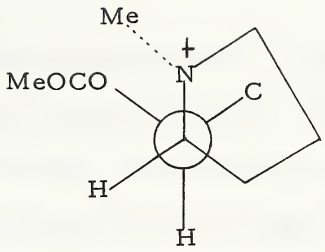
4a



4b



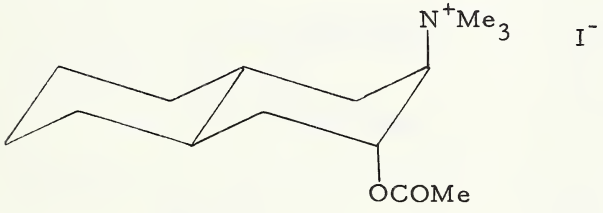
4a



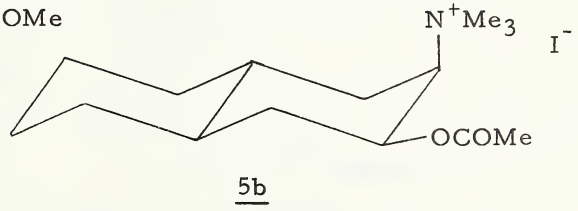
4b

nicotinic. This finding led the authors to suggest that the muscarinic and nicotinic receptors were stimulated by trans and gauche conformations of ACh respectively .

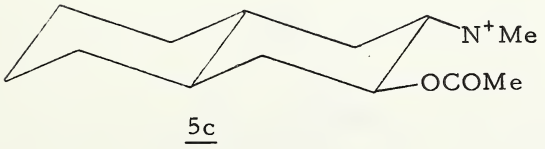
Similar investigations have been carried out by others. Smissman et al. (1966) synthesized four trans decalin analogs of ACh (5a - 5d) and among these diastereomers the trans-diaxial



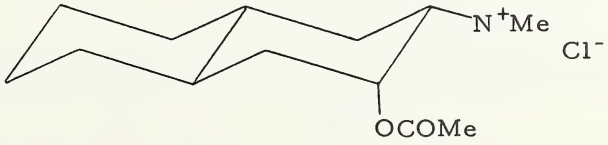
5a



5b



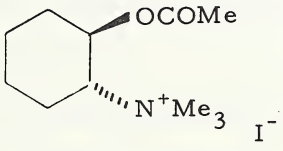
5c



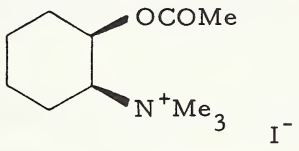
5d

possessed 0.06 percent of muscarinic potency of ACh. However, the nicotinic activity of these compounds was not reported. Since 5a is the only diastereomer which has its N^+Me_3 and OCOMe groups disposed in a trans fashion, it was proposed that the trans conformation was responsible for the muscarinic activity. An X-ray crystallographic study of 5a demonstrated that the torsion angle of ^+N-C-C-O was 147° (Shefter and Smissman, 1971), rather than a fully trans (180°) conformational angle.

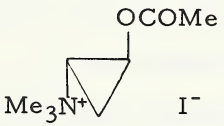
Cyclohexane (6), (Kay and Robinson, 1970), bicyclo [2,2,2]-octane (7) (Nelson and Wilson, 1971) and cyclopropane (8) (Armstrong and Cannon, 1970; Chiou et al., 1968) have also served as the ring skeletons for such analogs.



6a (±)

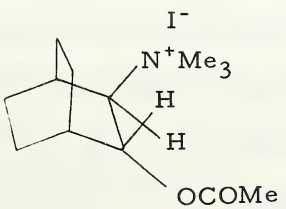


6b (±)

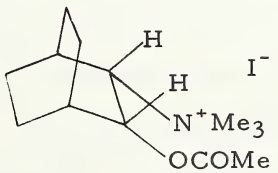


8a

8b



7a



7b

Among the diastereomeric pairs (6a, 6b and 7a ,7b) the trans-isomer in both cases demonstrated weak muscarinic activity; (±) 6a and 7a were found to be approximately 1/1000 and 1/37 as potent as ACh respectively while the corresponding cis isomers lacked any detectable activity. Compounds 6a and 6b were tested for nicotinic activity on the guinea pig ileum preparation, and found to be inactive. The nicotinic effect of 7b was not determined. Of particular interest is, the dextro isomer, (+)-trans-2-acetoxy-cyclopropyltrimethylammonium iodide (ACTM, 8a) which was as potent a muscarinic agent as ACh when tested on guinea pig ileum and 330 times more active than the corresponding levo isomers. The racemic cis-isomer 8b was expected to have nicotinic activity; however, only a negligible nicotinic effect on the frog rectus abdominis muscle was observed.

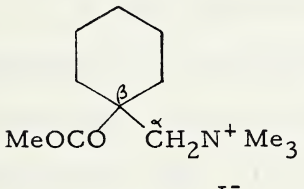
X-ray crystallographic studies of some potent muscarinic agents such as ACh, (+)-muscarine and choline established the gauche disposition of the $^{+}N/O$ functions in the solid state (Canepa et al., 1966). It was suggested that, in general, the torsion angle of $^{+}N-C-C-O$ of the ACh molecule lay between $+73^{\circ}$ and $+137^{\circ}$ for most muscarinic agents (Baker et al., 1971; Chothia and Pauling, 1968). Among the muscarinic agents studied, the torsion angle of ACh bromide was found to be $+77^{\circ}$ and that of the potent muscarinic agent, ACTM (8a), was found to be $+137^{\circ}$. On steric grounds the trans conformation of ACh should be the most stable conformation and is expected to be the preferred conformation especially when the

nitrogen and oxygen substituents are solvated. However, electrostatic interaction of the N^+ and O functions may offset the steric hindrance and allow ACh to exist as the gauche conformer. These results were supported by PMR studies of ACh in D_2O (Culvenor and Ham, 1966). The preferred gauche conformation was determined by the magnitude of coupling constants arising from a weighted average of all possible conformations, which excluded the trans as the favored form. IR studies, which will be discussed later, also supported these arguments. (Casy et al., 1971; Fellman and Fujita, 1966).

In summary, the evidence reported so far appears to support the idea that a transoid $^+$N-C-C-O disposition is involved in the interaction of ACh with muscarinic receptors even though the preferred conformation for this part of the ACh molecule is gauche. This suggests that a conformational change in the ACh molecule is induced upon interaction with the muscarinic receptor.

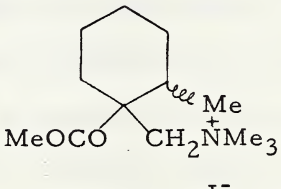
AIMS AND OBJECTIVES

It is well known that α-methylation of ACh decreases its muscarinic effects (Simonart, 1932). All rigid and semi-rigid ACh analogs so far reported are of the α/β dialkyl-substituted type, and generally exhibit a low order of muscarinic activity. It was, therefore, of interest to investigate some analogs, which were free of α-substitution and yet still subject to conformational restraint by introducing a cyclohexyl, or dimethyl substituent at the β-carbon of the ACh molecule. To this end, geometrically isomeric pairs of 2-, 3-, and 4-methyl-1-acetoxy-1-dimethylaminomethylcyclohexane methiodide, the corresponding desmethyl derivative (14a-14d) and acetyl-β,β-dimethylcholine iodide (16) have been prepared. The



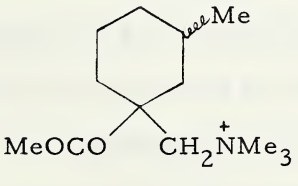
I^-

14a



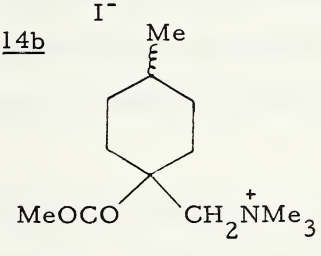
I^-

14b



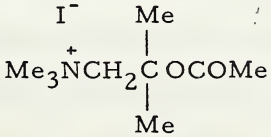
I^-

14c



I^-

14d

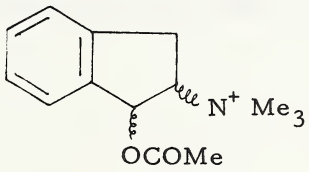


16

stereochemistry of these compounds has been studied and its relation to the muscarinic activities observed is discussed. The antagonistic activity of these compounds (against ACh) has also been studied.

This work has also been extended to include the following aspects:

1. Examination of ACh analogs which possess indanol as the ring skeleton.



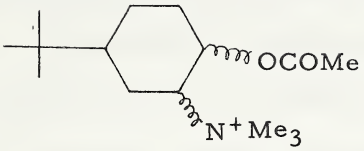
26 cis

30 trans

In α/β cyclic ACh analogs already studied, the activity is generally of a low order with the exception of the cyclopropyl derivatives (8a). It is, therefore, of interest to examine the indanol analogs (26, 30). The $^{+}$N-C-C-O dihedral angles of the analogs 26 and 30 closely correlate with those of the cis and trans cyclopropyl ACh analogs (8b and 8a), respectively, of which the latter has been reported to be as potent as ACh.

2. Investigation of 4-t-butylcyclohexanol analogs of ACh.

Derivatives of 2-aminocyclohexanol have already been studied (Kay et al., 1970). Insertion of a 4-butyl "anchor" leads to four possible RS-diastereoisomers (31-34) which provide a wider range of N-O substituents dispositions than do the disubstituted cyclohexyl analogs and it was considered that examination of the ACh analogs



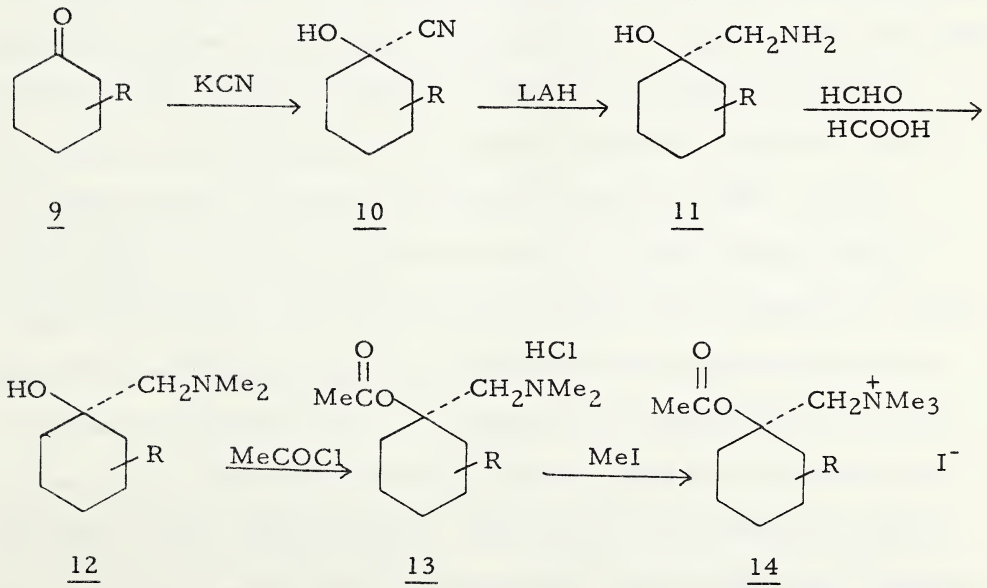
X^- = I, tosylate

31, 32, 33 and 34

(31-34) might lead to a clearer definition of the "active" $^+N/O$ conformation at muscarinic sites.

CHEMISTRY DISCUSSION

A general procedure was found for the synthesis of acetyl-β,β-dimethylcholine iodide (16) and some cyclohexyl analogs of acetylcholine. It involved the addition of potassium cyanide to the appropriate ketone to give a cyanohydrin which, upon reduction with lithium aluminum hydride, yielded a primary amine. The primary amine was heated with formic acid and formaldehyde to give the corresponding dimethylated tertiary amine. Esterification of the hydroxyl group of each tertiary amine with acetyl chloride afforded the amino-ester hydrochloride. The free base of each tertiary amino-ester was regenerated from its hydrochloride salt and treated with methyl iodide to give the quaternary ammonium ester. The general synthesis is depicted in Scheme 1.



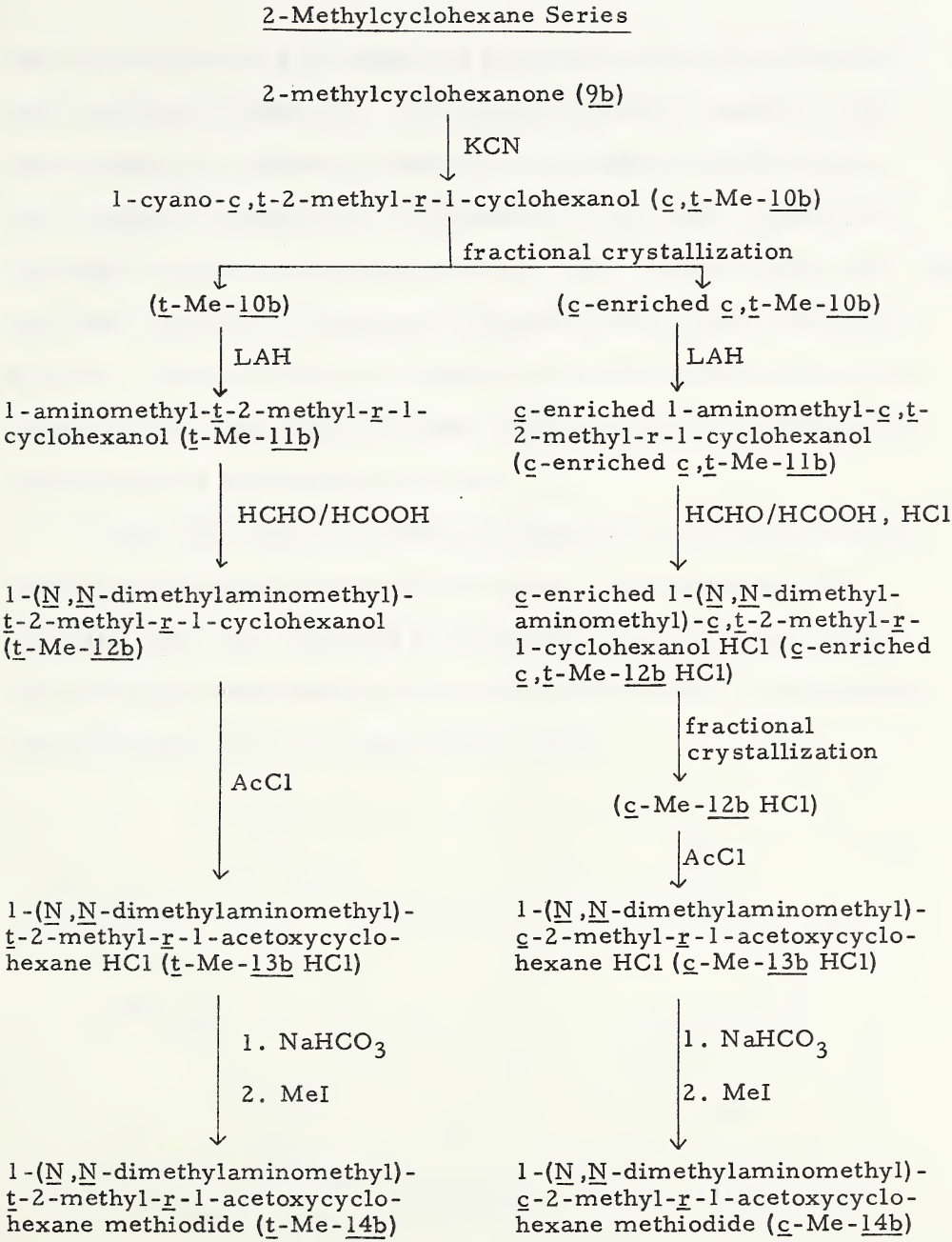
a, R = H b, R = 2-Me c, R = 3-Me d, R = 4-Me

Scheme 1

For cases where R=Me, attempts were made to separate cis-trans isomers at each stage by fractional crystallization monitored by PMR spectroscopy; the stages at which these were successful varied (Schemes 2-4). When one geometrical isomer was isolated, the second was sought after further reaction of residues enriched in that component. The nomenclature of these compounds followed the literature rules (Verkade et al. 1970).

2-Methylcyclohexane Series (see also Scheme 2)

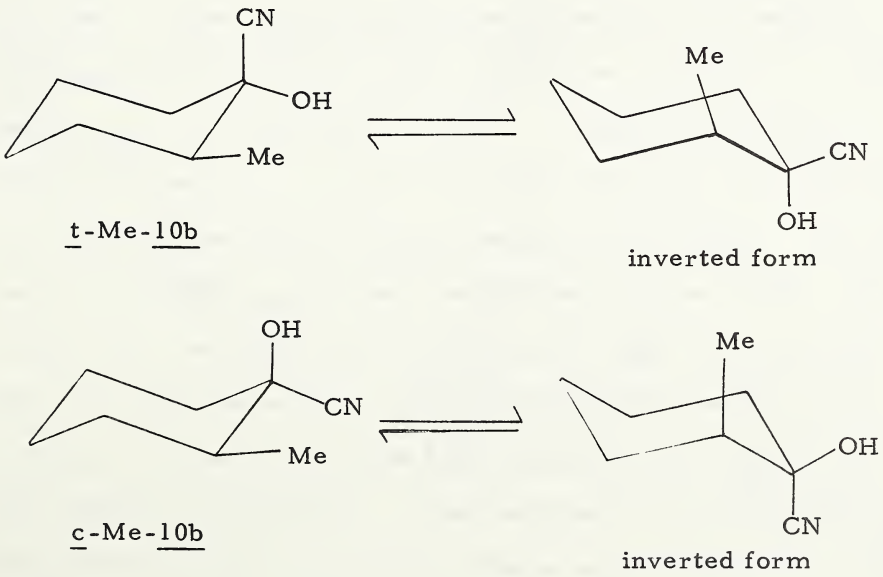
Addition of potassium cyanide to 2-methylcyclohexanone (9b) resulted in a mixture of cis and trans (Me/OH) 1-cyano-2-methyl-r-1-cyclohexanol (10b). The PMR spectrum of the total mixture of 10b in DMSO-d_6 exhibited two OH resonance signals at δ6.31 and 6.10 in an isomeric ratio of 3:1 as judged by the intensities of these two signals. Hydroxyl protons are strongly hydrogen bonded to this solvent and in this condition their chemical shifts are relatively insensitive to minor concentration and temperature variations and hence may be of value in configurational assignments (Chapman and King, 1964; Rader, 1966, 1969). The lower field OH resonance in the mixture 10b is assigned to an equatorial (eq) hydroxyl group on the grounds of: i) the deshielded nature of an eq as opposed to an axial (ax) environment in 6-membered alicyclic rings as a result of the deshielding cone of the carbon-carbon bond which deshields equatorial groups (Jackman and Sternhell, 1969; ApSimon et al., 1967) and ii) the probability of the more sterically accessible eq-OH being the more extensively hydrogen bonded to the solvent molecules (when a proton is so bonded it is deshielded (Pople et al., 1959)).


2-Methylcyclohexane Series
2-methylcyclohexanone (9b)
KCN
1-cyano-c,t-2-methyl-r-1-cyclohexanol (c,t-Me-10b)
fractional crystallization
(t-Me-10b)
(c-enriched c,t-Me-10b)
LAH
LAH
1-aminomethyl-t-2-methyl-r-1-cyclohexanol (t-Me-11b)
c-enriched 1-aminomethyl-c,t-2-methyl-r-1-cyclohexanol (c-enriched c,t-Me-11b)
HCHO/HCOOH
HCHO/HCOOH, HCl
1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-cyclohexanol (t-Me-12b)
c-enriched 1-(N,N-dimethylaminomethyl)-c,t-2-methyl-r-1-cyclohexanol HCl (c-enriched c,t-Me-12b HCl)
fractional crystallization
(c-Me-12b HCl)
AcCl
AcCl
1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-acetoxycyclohexane HCl (t-Me-13b HCl)
1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-acetoxycyclohexane HCl (c-Me-13b HCl)
1. NaHCO3
2. MeI
1. NaHCO3
2. MeI
1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-acetoxycyclohexane methiodide (t-Me-14b)
1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-acetoxycyclohexane methiodide (c-Me-14b)

Scheme 2

Thus all PMR spectra for which the OH signals were to be identified were recorded in DMSO-d_6. The major and minor isomers of 10b are assigned as 1-cyano-t-2-methyl-r-1-cyclohexanol (t-Me-10b) and 1-cyano-c-2-methyl-r-1-cyclohexanol (c-Me-10b), respectively. Fractional crystallization of the isomeric 10b resulted in pure t-Me-10b. The PMR spectrum of this isomer displayed one hydroxyl resonance at δ6.31. Pure 1-cyano-c-2-methyl-r-1-cyclohexanol could not be isolated at this stage and the mother liquor enriched in c-Me-10b was employed in the subsequent reactions.

Both t-Me-10b and c-Me-10b can exist as two conformational isomers by flipping of the cyclohexyl ring. It would appear that t-Me-10b and c-Me-10b would be the preferred conformers as they have two bulky substituents orientated equatorially and are therefore thermodynamically more stable (Eliel, 1962).



t-Me-10b

inverted form

c-Me-10b

inverted form

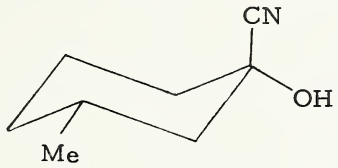
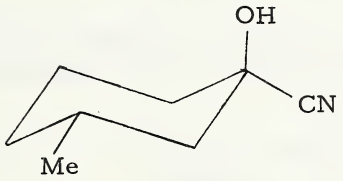
The validity of these arguments is confirmed by their leading to the correct assignment of the isomers 10b, of known configuration (Nazarov et al., 1958). 1-Aminomethyl-t-2-methyl-r-1-cyclohexanol (t-Me-11b) was prepared from isomerically pure t-Me-10b; the hydrochloride of t-Me-11b exhibited one OH PMR signal at δ4.93. A cis-enriched mixture 11b hydrochloride was made from the mixture 10b and its PMR spectrum displayed two distinct OH signals at δ4.93 and 4.68. Since pure 1-aminomethyl-c-2-methyl-r-1-cyclohexanol hydrochloride (c-Me-11b) could not be separated, the mixture was employed as the starting material to synthesize the isomeric 1-(N,N-dimethylaminomethyl)-c,t-2-methyl-1-cyclohexanol hydrochloride (c,t-Me-12b HCl). The PMR spectrum of c,t-Me-12b·HCl afforded two OH signals at δ4.77 and 5.08. Upon repeated crystallization the intensity of the signal at δ4.77 grew, while that of the signal at δ5.08 decreased. Pure 1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-cyclohexanol hydrochloride (c-Me-12b HCl) was separated. Its PMR spectrum gave one OH signal at δ4.77. 1-(N,N-Dimethylaminomethyl)-t-2-methyl-r-1-cyclohexanol hydrochloride (t-Me-12b HCl) was prepared from the pure trans precursor (t-Me-11b). Its PMR spectrum in DMSO-d_6 gave only one OH resonance at δ5.08. The tertiary amino-alcohols (c-Me-12b and t-Me-12b) were esterified with acetyl chloride to give 1-(N,N-dimethylaminomethyl)-c,t-2-methyl-r-1-acetoxycyclohexane hydrochloride (c-Me-13b HCl and t-Me-13b HCl, respectively). The free bases of c- and t-Me-13b were liberated with sodium bicarbonate solution and subsequently treated

with excess of methyl iodide to give isomeric 1-(N,N-dimethylaminomethyl)-c,t-2-methyl-r-1-acetoxycyclohexane methiodide (c and t-Me-14b, respectively). An alternate procedure to prepare the quaternary ammonium esters involved formation of a quaternary ammonium salt of a tertiary amino-alcohol prior to esterification. However, a quaternary ammonium acetate obtained by this procedure was usually impure and did not give the correct elemental analysis despite repeated crystallization.

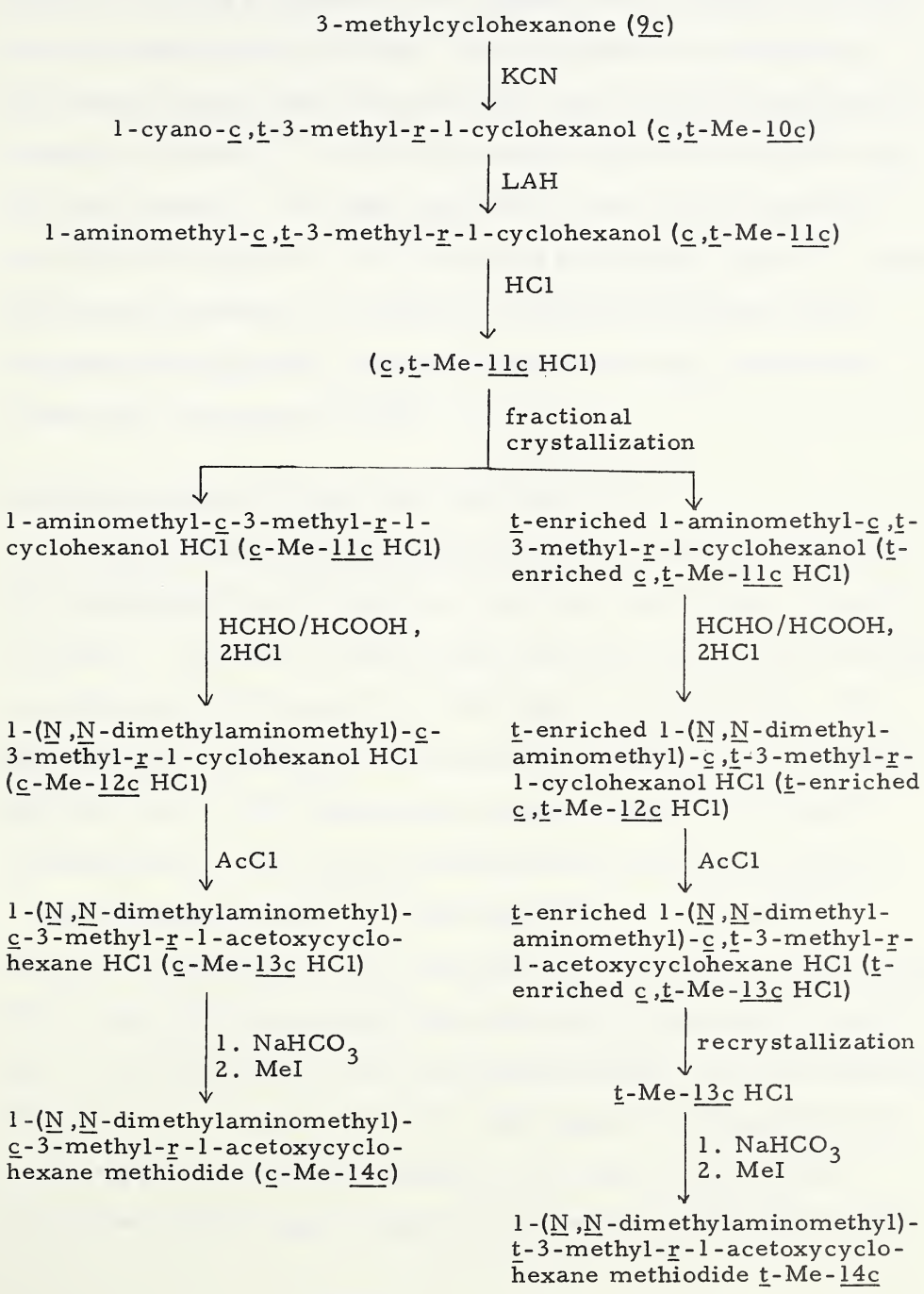
3-Methylcyclohexane Series (see also Scheme 3)

The configurational assignments of 1-cyano-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-10c) and isomeric 1-cyano-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-10d) were made in the manner described for the 2-methyl series, and are summerized in Table 1. An unsuccessful attempt was made to separate the component isomers from 10c with column chromatography, and the isomeric mixture was reduced to give a mixture of 1-aminomethyl-c,t-3-methyl-1-cyclohexanol (c,t-Me-11c). Fractional crystallization of the hydrochloride salt of c,t-Me-11c yielded the major isomer, 1-aminomethyl-c-3-methyl-r-1-cyclohexanol hydrochloride (c-Me-11c HCl), and this isomer was related to the major one in the isomeric cyanohydrin, i.e. 1-cyano-c-3-methyl-r-1-cyclohexanol. The PMR spectrum of c-Me-11c HCl displayed an OH signal at δ5.13 whereas that of the mixture showed the duplicate signals at δ5.13 and 4.77. The pure trans-isomer could not be isolated and, therefore, a mixture of the trans- and cis-

Table 1. Configurational Assignment and Isomeric Ratio of a Mixture of 10c, 10d.

Isomer and its preferred conformation	Isomeric ratio	Chemical Shift (δ) of OH signal in DMSO-d_6
	3	6.45
	1	6.15
	3	6.40
	1	6.15

3-Methylcyclohexane Series

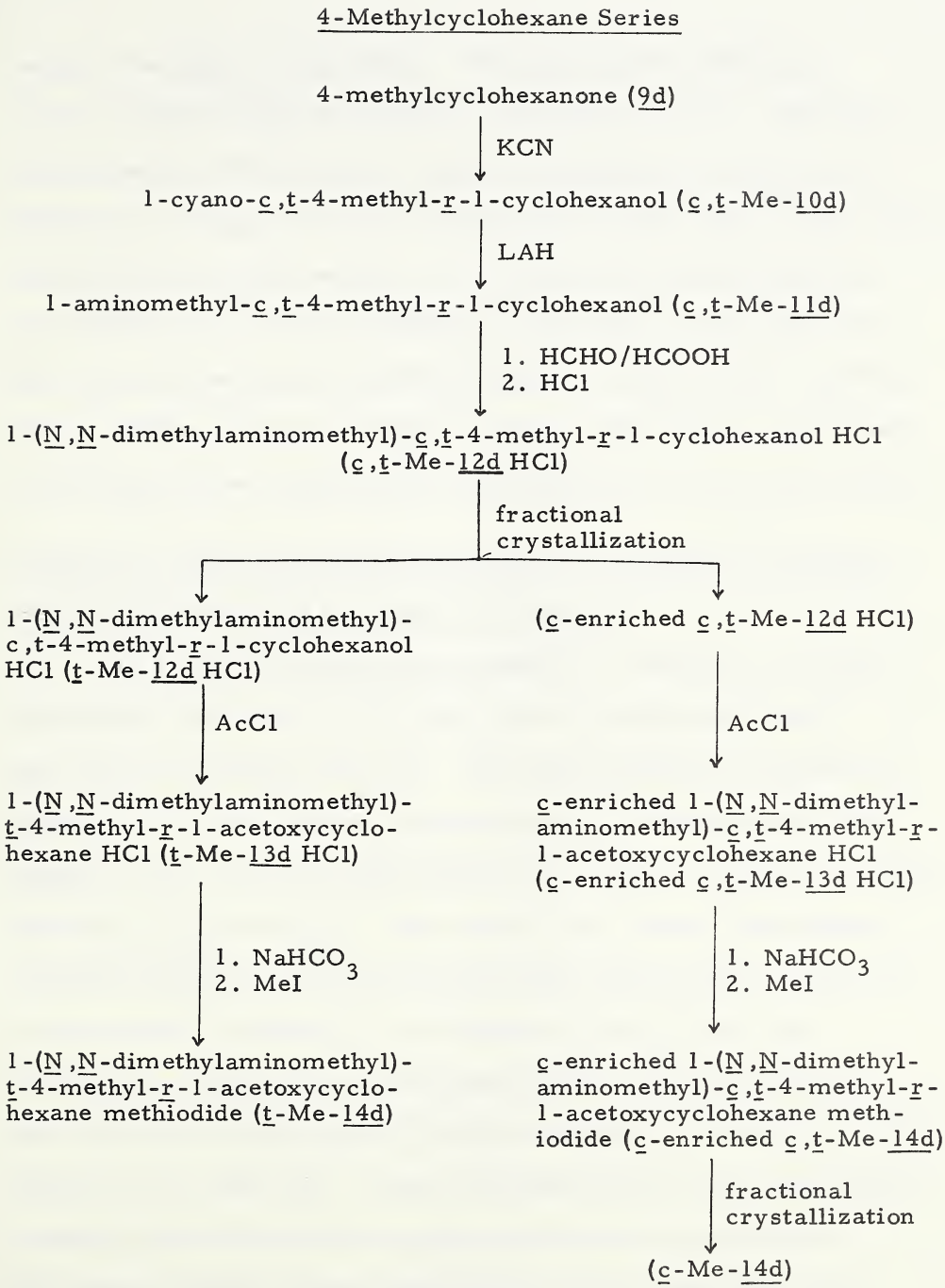


Scheme 3

isomers was used to synthesize the dimethylamino-alcohols, and then the amino-ester hydrochlorides. Upon repeated crystallization of the isomeric amino-ester hydrochloride, pure 1-(N,N-dimethylaminomethyl)-t-3-methyl-r-1-acetoxycyclohexane hydrochloride (t-Me-13c HCl) was isolated. The PMR spectrum of t-Me-13c HCl displayed one acyl methyl signal at δ2.12, while the acyl methyl signal of 1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (c-Me-13c HCl), prepared from the pure cis- precursor (c-Me-11c), resonated at δ2.08.

4-Methylcyclohexane Series (see also Scheme 4)

The configurational assignments of the 1-cyano-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-10d) have been described earlier and given in Table 1. Attempts to separate the component isomers by fractional crystallization of the mixture c,t-Me-10d were unsuccessful. The hydrochloride of isomeric 1-aminomethyl-4-methyl-r-1-cyclohexanol (c,t-Me-11d) was very hygroscopic and not suitable for fractional crystallization. Pure 1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-cyclohexanol hydrochloride (t-Me-12d·HCl) was separated by repeated crystallization of the cis-trans isomeric mixture c,t-Me-12d HCl. The latter was prepared from the isomeric precursor, c,t-Me-11d. The PMR spectrum of t-Me-12d HCl showed only one methylene (CH_2N) resonance signal at δ3.33. The signal corresponded to the major signal in the isomeric mixture (δ3.33 and 3.19), and was correlated with the major isomer of the mixture c,t-Me-10d already


4-Methylcyclohexane Series
4-methylcyclohexanone (9d)
KCN
1-cyano-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-10d)
LAH
1-aminomethyl-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-11d)
1. HCHO/HCOOH
2. HCl
1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-cyclohexanol HCl
(c,t-Me-12d HCl)
fractional crystallization
1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-cyclohexanol HCl (t-Me-12d HCl)
(c-enriched c,t-Me-12d HCl)
AcCl
AcCl
1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-acetoxycyclohexane HCl (t-Me-13d HCl)
c-enriched 1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-acetoxycyclohexane HCl (c-enriched c,t-Me-13d HCl)
1. NaHCO3
2. MeI
1. NaHCO3
2. MeI
1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-acetoxycyclohexane methiodide (t-Me-14d)
c-enriched 1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-acetoxycyclohexane methiodide (c-enriched c,t-Me-14d)
fractional crystallization
(c-Me-14d)

Scheme 4

assigned the trans configuration. The cis-isomer could not be isolated until the stage of quaternary ammonium esters. Repeated crystallization of the isomeric 1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-acetoxycyclohexane methiodide (c,t-Me-14d) provided the second isomer of the 4-methyl series, i.e. 1-(N,N-dimethylaminomethyl)-c-4-methyl-r-1-acetoxycyclohexane methiodide (c-Me-14d) which was characterized by several PMR signals: 4-Me, δ0.87; OCOMe, δ2.15; N^+Me_3, δ3.23 and CH_2N, δ3.93. This isomer was related to c-Me-10d whose configuration was established as described earlier.

(+) and (-)-1-(N,N-Dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane Methiodide (+) and (-)-(c-Me-14c)

(+)-1-(N,N-Dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (+)-(c-Me-14c) was synthesized using optically pure starting material. The total synthesis is depicted in Scheme 5. (+)-3-Methylcyclohexanone was treated with potassium cyanide to give a cis and trans mixture of 1-cyano-3-methyl-r-1-cyclohexanol (+)-(c,t-Me-10c). The mixture was reduced with lithium aluminum hydride to give the corresponding cis and trans mixture of 1-aminomethyl-3-methyl-r-1-cyclohexanol (+)-(c,t-Me-11c). Fractional crystallization of the hydrochloride salt of the isomeric pair led to the isolation of (+)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol (+)-(c-Me-11c). These compounds had a very small optical rotation, and could not be accurately determined by polarimetry. Thus optical rotatory dispersion curves of these compounds were

(+)-1-(N,N-Dimethylaminomethyl)-r-3-methyl-r-1-acetoxycyclohexane Methiodide (+)-(c-Me-14c)

(+)-3-methylcyclohexanone (−)-(9c)

↓ KCN

1-cyano-c,t-3-methyl-r-1-cyclcohexanol (c,t-Me-10c)

↓ LAH

1-aminomethyl-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-11c)

↓ HCl

c,t-Me-11c HCl

↓ fractional crystallization

1-aminomethyl-c-3-methyl-r-1-cyclohexanol HCl (c-Me-11c HCl)

↓ NaOH

(+)-1-aminomethyl-c-3-methyl-r-1-cyclohexane (+)-(c-Me-11c)

↓ 1. HCHO/HCOOH
2. HCl

(+)-1-N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol HCl (+)-(c-Me-12c HCl)

↓ AcCl

(+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane HCl (+)-(c-Me-13c HCl)

↓ 1. $NaHCO_3$
2. MeI

(+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (+)-(c-Me-14c)

Scheme 5

recorded to indicate optical purity. It was noted on the optical rotatory dispersion curves that the optical rotations were usually small at the wavelength of sodium light (namely 589 nm) and were masked by the noise of the instrument. It was therefore, found desirable to record the optical rotation at a wavelength near the ultraviolet region. A wavelength of 260 nm was then chosen for this study. (+)-1-Aminomethyl-c-3-methyl-r-1-cyclohexanol (+)-(c-Me-10c) prepared from (+)-3-methylcyclohexanone had $[\alpha]^{25^{\circ}}_{260\ nm}$ + 13° (c, 0.4, H_2O). The subsequent reactions carried out on this compound, such as N,N-dimethylation, esterification, and quaternization, do not affect the disposition of the substituents at the asymmetric centre.

The synthesis of (-)-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (-)-(c-Me-14c) was accomplished using the optically pure precursor, (-)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol (-)-(c-Me-10c) (see Scheme 6). (-)-c-Me-10c was separated from the racemic mixture as a salt of d-tartaric acid. d-Tartaric acid was found to be an ideal resolving agent in this instance. Recrystallization of the diastereomeric salt five times gave the pure (-)-1-aminomethyl-c-3-methyl-r-cyclohexanol d-tartarate. The optical rotatory dispersion curve of the liberated base was used as a criterion of the optical purity.

(-)-1-(N,N-Dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane Methiodide (-)-(c-Me-14c)

3-methylcyclohexanone (9c)

↓ KCN

1-cyano-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-10c)

↓ i LAH
ii fractional crystallization

1-aminomethyl-c-3-methyl-r-1-cyclohexanol (c-Me-11c)

↓ d-tartaric acid

1-aminomethyl-c-3-methyl-r-1-cyclohexanol·d-tartarate

↓ crystallization 5 times

(-)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol ·d-tartarate

↓ NaOH

(-)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol (-)-(c-Me-11c)

↓ 1. HCHO/HCOOH
2. HCl

(-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol HCl
(-)-(c-Me-12c HCl)

↓ AcCl

(-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane HCl (-)-(c-Me-13c HCl)

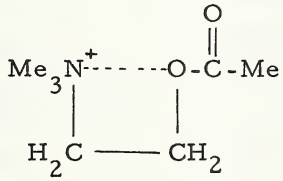
↓ 1. $NaHCO_3$
2. MeI

(-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide
(-)-(c-Me-14c)

Scheme 6

IR Dilution Studies of $\tilde{\nu}_{C=O}$ of Cyclohexyl ACh Analogs

Several IR studies have established that the carbonyl stretching mode ($\tilde{\nu}_{C=O}$) of ACh is higher than that of the corresponding tertiary amine and of ethyl acetate (Fellman and Fugita, 1966; Canepa and Mooney, 1965). The shift to higher wavenumbers, which occurs when a β-hydrogen of ethyl acetate is replaced by a trimethylammonium group may be interpreted in terms of electronic interaction between the positively charged nitrogen and a lone pair of electrons of the ether



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oxygen atom. This interaction induces an electron drift from the carbonyl oxygen (via the ether oxygen) to the nitrogen atom, which opposes the polarization of the carbonyl group with a consequent rise in its absorption frequency (Martin-Smith, 1967). An interaction of this type requires proximity of the charged nitrogen and ester functions, and its demonstration provides support for gauche $^{+}$N/O conformers for ACh and its congeners. To determine if this electronic interaction also operates in the cyclohexyl ACh analogs to give a preferred gauche $^{+}$N/O conformation, the IR data of these compounds were recorded in chloroform at concentrations varying from 0.1% to 3%. In dilute chloroform solutions the undesired solute-solvent interaction and intermolecular interactions can be avoided (Casy et al., 1971;

Table 2 Carbonyl Stretching Frequencies of Some ACh Analogs in Chloroform.

No.	Compound	$\nu_{C=O}$ (cm^{-1}) 3%	0.3%	0.1%	$\Delta\nu_{C=O}$[d]
1	a	1720	1720		
2	b	1720	1720		
3	c	1746	1746		26
4	14a	1737	1735	1735	15
5	c-Me-14b		1735		15
6	t-Me-14b	1735	1735	1738	15
7	t-Me-14c		1735		15
8	t-Me-14c		1735	1735	15
9	c-Me-14c		1735		15
10	t-Me-14d		1735		15
11	e			1735	11
12	ACh			1755	20

a Cyclohexyl acetate

b 1-(N,N-Dimethylaminomethyl)cyclohexyl acetate

c Acetyl-β,β-dimethylcholine

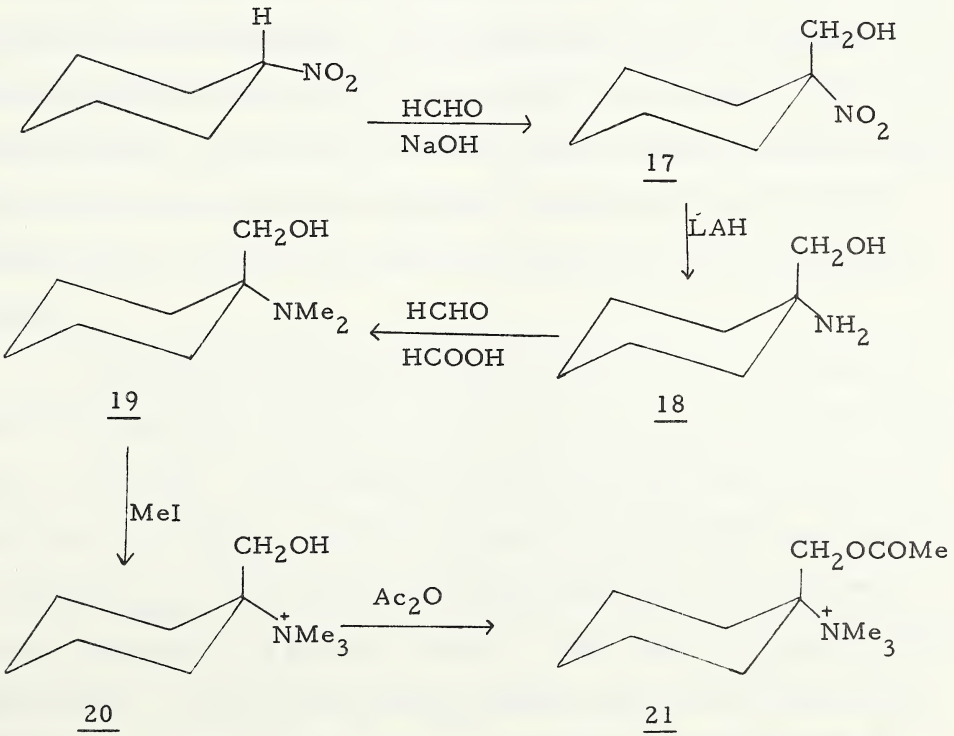
d $\nu_{C=O}$(compound) - $\nu_{C=O}$ compound a

e Ethyl acetate

Tichy, 1965). In all cases, an increase in wavenumbers of $\nu_{C=O}$ by 15 cm^{-1} in these compounds relative to cyclohexyl acetate is observed (see Table 2). For acetylcholine and acetyl-β,β-dimethylcholine an increase of 25 and 11 cm^{-1} relative to ethyl acetate is found, respectively. These results provide evidence that gauche $^{+}$N/O conformations are adopted by the cyclic ACh analogs.

(1-N,N-Dimethylaminocyclohexyl)methyl Acetate Methiodide (21)

(1-N,N-Dimethylaminocyclohexyl)methyl acetate methiodide (21) was prepared following essentially the same procedure reported by Wheatley (1954). The synthesis is depicted below (Scheme 7).



Scheme 7

(1-Nitrocyclohexyl)methanol (17) was prepared by condensation of nitrocyclohexane with formaldehyde in the presence of sodium hydroxide. In the literature the preparation of (1-aminocyclohexyl)-methanol (18) was accomplished by high pressure hydrogenation of the nitro compound 17 in 43% yield (Wheatley, 1954). In the present case this compound was prepared using lithium aluminum hydride as reducing agent for two reasons. Firstly, there is a literature method (Parham and Ramp, 1951) by which 2-nitrobutane can be reduced to 2-aminobutane using lithium aluminum hydride, and the analogous reduction should be applicable to (1-nitrocyclohexyl)methanol (17). Secondly, a high pressure hydrogenation apparatus was not available at the time of investigation. It was found that the use of lithium aluminum hydride was superior to catalytic hydrogenation in the present study. It offered a relatively simple method of synthesizing (1-aminocyclohexyl)methanol (18) and, in addition, it gave a better yield, (58% as compared to 43% yield obtained by catalytic hydrogenation).

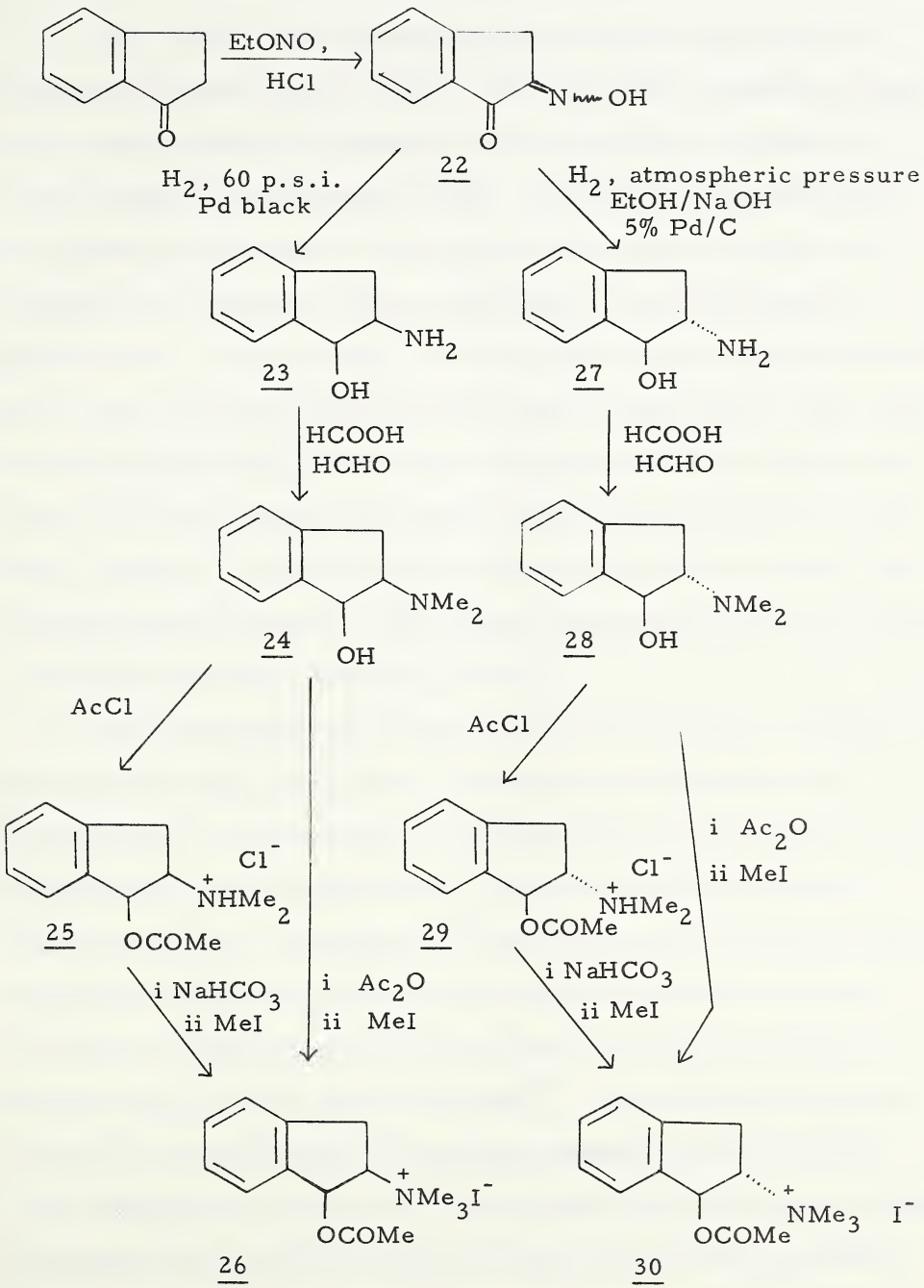
Formaldehyde and formic acid methylation of (1-aminocyclo-hexyl)methanol (18) afforded 1-(N,N-dimethylaminocyclohexyl)methanol (19) in 64% yield. Compound 19 was subsequently converted into its methiodide salt (20). The PMR spectrum of 20 in DMSO-d_6 displayed a triplet (J_{HCOH} = 4.7 Hz) at δ5.40 characteristic of the hydroxyl proton resonance of a primary alcohol. This signal disappeared after deuteration. The hydroxyl proton coupling could not be observed in the PMR spectrum of the primary amino-alcohol hydrochloride 18

recorded in the same solvent. The lack of H-C-O-H coupling in the case of the primary amino-alcohol hydrochloride may be ascribed to rapid proton exchange catalyzed by the basic feature of an amino-alcohol hydrochloride, which dissociates in the solvents (Bass and Sewell, 1969). However, when the basic character of (1-aminocyclohexyl)methanol was removed by quaternization, hydroxyl H-C-O-H coupling was observed.

Esterification of the (1-N,N-dimethylaminomethylcyclohexyl)-methanol methiodide was easily achieved by stirring this compound in acetic anhydride at room temperature. In contrast, 1-(N,N-dimethylaminomethyl)cyclohexanol methiodide (20a) did not react with acetic anhydride even after heating for a period of 2-6 hr. A catalyst (zinc chloride) was found necessary to initiate esterification, and the product obtained in this manner was contaminated with impurities which were difficult to remove. The difference in reactivity reflects the hindered nature of the hydroxyl group in the tertiary alcohol 20a.

c-1-Acetoxy-2-dimethylaminoindan Methiodide (26) and t-1-Acetoxy-2-dimethylaminoindan Methiodide (30)

Reduction of 2-hydroxyimino-1-indanone (22) under somewhat similar conditions has been reported to lead to either c or t-2-amino-1-hydroxyindan (Huebner, 1970, Rosen and Green, 1963). These compounds can be converted to the desired product through the series of steps shown in Scheme 8.

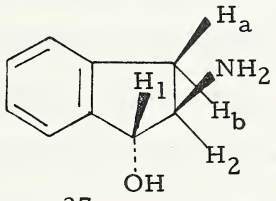

EtONO,
HCl
N OH
O
22
H2, 60 p.s.i.
Pd black
H2, atmospheric pressure
EtOH/Na OH
5% Pd/C
NH2
OH
23
27
HCOOH
HCHO
NMe2
24
28
AcCl
Cl⁻
+
NHMe2
OCOMe
25
29
i NaHCO3
ii MeI
i Ac2O
ii MeI
+
NMe3I⁻
26
30

Scheme 8

The synthesis of 2-hydroxyimino-1-indanone (22) was first reported by Huebner et al. (1962). The procedure involved aerating an alcoholic solution of 1-indanone with amyl nitrite, followed by a careful addition of hydrochloric acid. The product separated from the solution in 48% yield. In the present work this procedure was modified in an attempt to improve the yield. The modifications applied were: i) hydrochloric acid was added to the indanone solution prior to the treatment with the nitrite, and ii) ethyl nitrite rather than amyl nitrite was employed because the former could be readily made from a reaction of ethanol and sodium nitrite in the presence of acid. Thus 1-indanone and hydrochloric acid were dissolved in ethanol and aerated with ethyl nitrite. The product precipitated out of the solution as it formed and 86% yield was achieved.

Employing different solvent systems both c- and t-2-amino-1-hydroxyindane (23) and (27) were obtained by hydrogenation of 2-hydroxyimino-1-indanone (22). Compound 22 was not soluble in ethanol, thus hydrogenation of this compound was carried out in a mixture of ethanol and 5% aqueous sodium hydroxide solution at room temperature and atmospheric pressure with 5% Pd/C as catalyst. t-2-Amino-1-hydroxyindan was formed and had a m.p. 104-105° (Huebner et al., 1970 reported 100-103°). The corresponding cis-isomer 23 was prepared by a literature method (Rosen and Green, 1963) using glacial acetic acid as solvent and 100% Pd black as catalyst. A hydrogen pressure of 30-45 p.s.i. was employed and the product melted at 102-104° (Rosen and Green, 1963, gave 105-109). Since

the melting points of the isomeric pair were so close, a positive identification on this basis could not be made. Rosen and Green (1963) concluded that the aminoindanol prepared by this method was the trans-isomer. Rosen et al. (1964) considered that the observed coupling constants, $J_{H_1H_2}$ (5.4 Hz) and $J_{H_bH_2}$ (6.2 Hz), differed too much to arise from the cis-isomer 23. It was argued that if the compound



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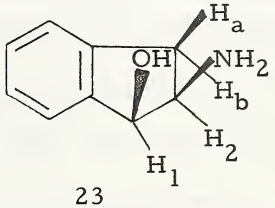
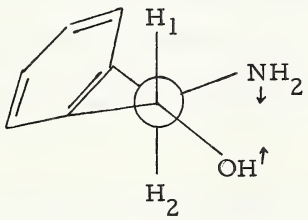


23

had a cis configuration, $J_{H_1H_2}$ and $J_{H_bH_2}$ should be the same, as predicted by the Karplus equation (Karplus, 1959, 1963). Unfortunately these authors did not make the other isomer to obtain comparative J data. Huebner et al. (1970) investigated this problem using chemical methods and IR spectroscopy in addition to PMR spectroscopy. They observed that both isomers displayed a free (near 3660 cm^{-1}) and bonded (near 3590 cm^{-1}) hydroxyl band in the IR spectra; dilution studies in methylene chloride established that one band arose from intermolecular hydrogen bonding and the other from intramolecular (the latter band was unchanged on dilution). The isomer exhibiting intramolecular hydrogen bonding was assigned a cis configuration (23), and that showing intermolecular hydrogen bonding, a trans (27). The latter corresponded to the "cis" isomer of Rosen et al. (1964). Our assignments agree with those proposed by Huebner et al. (1970).

The use of coupling constants for stereochemical studies in the indanol series may be deceptive because a slight ring deformation may change the dihedral angle of vicinal protons, and hence alter their coupling constants. The fact that the cis-isomer (correctly established) had $J_{H_1H_2}$ of 5.4 Hz suggested that these two protons were not fully eclipsed. It is well known that the J_{vic} value of a perfectly eclipsed vicinal pair is around 8-9 Hz (Karplus, 1959). For the trans-isomer, if the dihedral angle of the vicinal protons were 120°, the $J_{H_1H_2}$ would be 2-3 Hz or less. But, since $J_{H_1H_2}$ was found to be 5.8 Hz, the dihedral angle must be greater than 120°, with both hydroxyl and amino group twisted towards each other as shown below. Thus, it is



easier to incorporate J_{vic} values into an aminoindanol whose configuration is already known, than to deduce an unknown configuration based on J_{vic} values. However, in the present study, it was found that the use of H_1 and H_2 chemical shifts successfully corroborated the configurational assignment of the aminoindanols. The PMR spectra of c- and t-1-acetoxy-2-dimethylaminoindan hydrochloride, (25 and 29) were examined. The methine H_1 signal of the trans-isomer 29 was found to be 0.5 ppm downfield from that of the corresponding cis-isomer 25 (δ6.76 vs 6.26). This observation may be ascribed to the

strong deshielding effect of the $^{+}NHMe_2$ group which acts on H_1 through space. The Dreiding model of the cis- and trans- molecules showed that H_1 of the trans-isomer was in close proximity to the $N^{+}HMe_2$ group, while that of the cis-isomer was remote from the same substituent. This deshielding effect was expected to be less prominent in the free base which lacks the full positive charge of the protonated species. Indeed, when a drop of sodium hydroxide solution (10%) was added to the PMR sample of the trans-isomer 29 in DMSO-d_6, the H_1 signal shifted upfield by 0.46 ppm (from δ6.76 to 6.30), whereas with the corresponding cis-isomer 25 the addition of sodium hydroxide solution shifted the H_1 signal upfield only by 0.11 ppm (from δ6.26 to 6.15). The small change in the chemical shift of the cis-isomer was understandable as H_1 was further removed from the $N^{+}HMe_2$ and so was less sensitive to a change in its deshielding effect.

The free base of the tertiary amino-ester hydrochloride was liberated and treated with methyl iodide. However, the trans-isomer 29 was found to be partially hydrolyzed to the alcohol despite all precautions taken to avoid hydrolysis. The cause of the hydrolysis was unknown. Perhaps the acetoxyl group of the trans-isomer 29 was less hindered and more available to a hydroxylating species than was the cis-form. An alternate procedure was therefore devised to prepare the quaternary ammonium salts 26 and 30. Thus, the tertiary aminoindanol was stirred with acetic anhydride for a period of 7 days followed directly by treatment with methyl iodide. The desired

product separated from the solution as it formed. The PMR spectrum of the trans-isomer 30 displayed two methine signals, H_1 (δ6.81, J_{vic} = 5.0 Hz), and H_2 (δ4.75 an apparant quartet not well resolved). Both signals were at lower field than those of the corresponding cis-isomer 26 (δ6.37 and 4.53). Again, this was attributed to the deshielding effect of the trimethylammonium and acetoxyl groups.

PHARMACOLOGY

Methods

Guinea - pig Ileum Preparation

(1) Determination of Parasympathomimetic Activity

The guinea - pigs (300-500 g) were killed and a segment of the ileum (2-3 cm) isolated and suspended in a 20 ml tissue bath filled with modified Kreb's solution aerated with 95% oxygen and 5% carbon dioxide at 37°. The composition of Kreb's solution (g/l) was: NaCl, 6.9; KCl, 0.35; $CaCl_2$, 0.28; $NaHCO_3$, 2.1; KH_2PO_4, 0.61; $MgSO_4 \cdot 7H_2O$, 0.29; and glucose, 2.0. The agonistic activity was tested according to a reported method, (Edinburgh Staff, 1968). A two minute cycle was allowed for the guinea-pig ileum experiment: 0 sec- drug in; 30 sec - wash for 10 sec; 60 sec - wash for 10 sec; 70-120 sec - rest period. ACh was given in at least three concentrations of 0.005 - 0.01 μg/ml, and the compounds were given in concentrations up to 200 μg/ml. Muscle contractions were recorded using an isotonic ink-writing lever. Dose-response curves to ACh and the test compounds were obtained. The equimolar potencies of the compounds and ACh were calculated using a four point assay. Hyoscine hydrobromide (0.01 μg/ml) and hexamethonium chloride (10 μg/ml) were used to block muscarinic and nicotinic receptors respectively.

(2) Determination of Parasympatholytic Activity

The antagonistic activity was tested as follows: control dose-response curves to ACh (0.005-0.01 μg/ml) and 1,1-dimethyl-4-

phenylpiperazinium iodide (DMPP) (0.5-2.0 μg/ml) were first obtained, and the preparation was then exposed to the test compound by replacing Kreb's solution with Kreb's solution containing the compound (10 μg/ml). The dose-response curves of ACh and DMPP were again determined.

(3) Investigation of the Mechanism of the Parasympathomimetic Action of the Compounds

The guinea-pig ileum experiment was set up in a manner similar to that described for the determination of muscarinic activity. The control dose-response curves of ACh and the test compounds were first obtained, and the preparation was then treated with blocking agents in Kreb's solution. The dose-response curves of ACh and the test compounds were again obtained. These blocking agents were: chlorpheniramine maleate (10 μg/ml), DMPP (25 μg/ml), lidocaine hydrochloride (10 μg/ml), morphine hydrochloride (50 μg/ml), nicotine (20 μg/ml), pentolinium tartrate (25 μg/ml), procaine hydrochloride (25 μg/ml), hexamethonium chloride (25 μg/ml), serotonin (100 μg/ml) and tetrodotoxin (0.1 μg/ml). In most cases, the preparation was then washed to remove the blocking agent and the dose-response curves repeated. In some cases, for example, tetrodotoxin experiments, this washing process failed to reverse the blockade produced.

The experiments were also carried out at 37°, 25° and 18° for the test compound, ACh and DMPP.

(4) Denervation Studies

A procedure reported by Chiou and Long (1969) was used in this study. Segments of the guinea-pig ileum (2-3 cm) were stored in modified Tyrode's solution at 2^{o} for 24 hr, 48 hr and 72 hr respectively. After the period of storage, the segment was suspended in Tyrode's solution gassed with 95% oxygen and 5% carbon dioxide at 10^{o}. The composition of the solution is (g/l): NaCl, 8.0; KCl, 0.2; $CaCl_2$, 0.2; $MgCl_2$, 0.1; NaH_2PO_4, 0.05; $NaHCO_3$, 1.0; and dextrose, 2.0. ACh, nicotine, DMPP and the test compounds were given and responses noted.

Frog Rectus Abdominis Muscle Preparation

(1) Determination of Nicotinic Activity

Frogs (Rana pipiens) of either sex, weighing about 20 g were pithed. The skin of the abdomen was removed and a rectus muscle was isolated. The muscle was mounted in a 20-ml bath filled with 70% Kreb's solution (70 ml of Kreb's solution diluted with distilled water to 100 ml) aerated with 95% oxygen and 5% carbon dioxide at room temperature. ACh was given at concentrations between 0.2-0.5 μg/ml and the compounds were administered at concentrations up to 100 μg/ml. Muscle contractions were recorded using as isotonic ink-writing lever. A 5 minute cycle was used for the experiments: -30 sec - drum starts; 0 sec - drug in; $1\frac{1}{2}$ min - drum stops and wash for 10 sec; $2\frac{1}{2}$ min - wash for 10 sec; -30 sec drum starts. The dose-response curves of ACh and the test compounds were

obtained, and the activity, if any, was measured using a four point assay (Edinburgh Staff, 1968).

(2) Determination of Anti-nicotinic Activity

The antinicotinic activity of the compounds on the rectus muscle was studied in the following manner: dose-response curves to ACh were obtained as a control, the preparation was then immersed in solutions containing the compound (0.2-50 μg/ml) and the dose-response curve to ACh repeated. Gallamine triethiodide (10 μg/ml) was used as a reference compound. The affinity constants of the compounds and gallamine were obtained as dose ratios of ACh divided by concentration of antagonists using a four point assay (Edinburgh Staff, 1968).

Results and Discussion

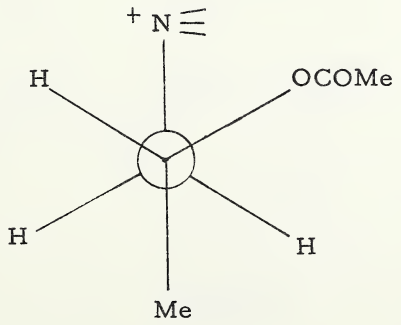
Acetyl β,β-dimethylcholine (16), desmethyl and cis and trans 2, 3 and 4-methyl substituted cyclohexyl ACh analogs (14a, 14b, 14c, 14d) were first evaluated for their parasympathomimetic effect on the guinea-pig ileum. Details of the pharmacological results are given in Table 3. For the β,β-disubstituted type analogs, only acetyl β,β-dimethylcholine (16), and 1-(N,N-dimethylaminomethyl)-c-3-methyl r-1-acetoxycyclohexane methiodide (c-Me-14c) (the latter probably acts indirectly and will be discussed separately) demonstrated feeble parasympathomimetic activity since their effect was abolished if the preparation was pretreated with hyoscine hydrobromide (0.01 μg/ml) but not hexamethonium chloride (10 μg/ml). Hyoscine hydrobromide

Table 3 ACh Agonistic and Antagonistic Activities of Substituted ACh Analogs[a]

Compounds	Agonistic Activity (guinea -pig ileum) Equimolar potency ACh = 1	Antagonistic Activity (Frog rectus muscle) Gallamine triethiodide = 1
14a	Inactive	3.3×10^{-2}
c-Me-14b	Inactive	4.7×10^{-2}
t-Me-14b	Inactive	3.9×10^{-2}
c-Me-14c	0.55×10^{-4}	2.5×10^{-2}
t-Me-14c	Inactive	3.6×10^{-2}
(+)-c-Me-14c	1.06×10^{-4}	2.5×10^{-2}
(-)-c-Me-14c	Inactive	2.8×10^{-2}
c-Me-14d	Inactive	3.6×10^{-2}
t-Me-14d	Inactive	2.5×10^{-2}
16	4.0×10^{-4}	2.2×10^{-2}
21	1.1×10^{-4}	Inactive
26	Inactive	Inactive
30	Inactive	Inactive
31	Inactive	5.3×10^{-2}
32	Inactive	3.6×10^{-2}
33	Inactive	7.5×10^{-2}
34	1.2×10^{-5}	1.5×10^{-2}
38[b]	Inactive	-
40[b]	Inactive	-

[a] Each value represents the average of four or more determinations.
[b] Noncompetitive antagonist.

is known to block specifically at muscarinic receptors. Their activity was of a low order, between $\frac{1}{2000}$ and $\frac{1}{10000}$ that of ACh. The activity for acetyl β,β-dimethylcholine iodide agrees with that given by Cocolas et al. (1970). Thus, β,β-dimethylation of ACh or introduction of a cyclohexyl group in the β,β-position of this molecule greatly reduces its muscarinic activity on the guinea-pig ileum. It has been well documented that a trans or near-trans $^{+}N/O$ conformation for ACh is the active form that interacts with the muscarinic receptors. Examples of these are some conformationally rigid analogs of ACh such as trans decalin analog 5a (Smissman et al. 1966), trans ACTM (8a). Our results seem to support the finding of these workers. It has been found that the preferred solute conformation of acetyl β-methylcholine (41) is gauche $^{+}N/O$ form (Casy et al., 1971), and it is probable that similar conformers are favored for acetyl β,β-dimethylcholine (16) and the equivalent forms (42-44) as supported by the IR evidence discussed before (see page 25).



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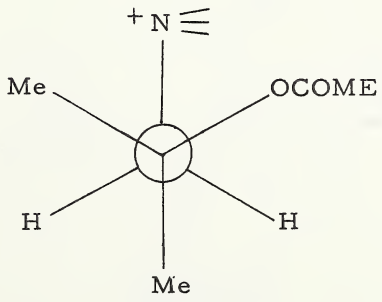

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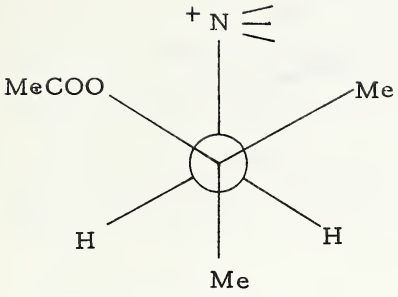

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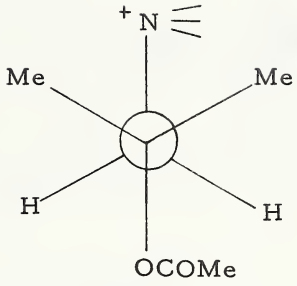
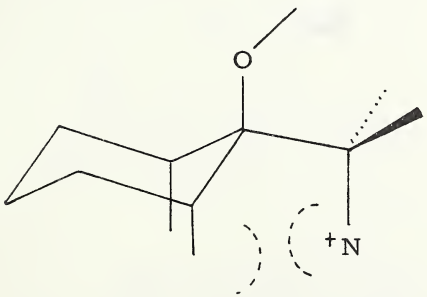
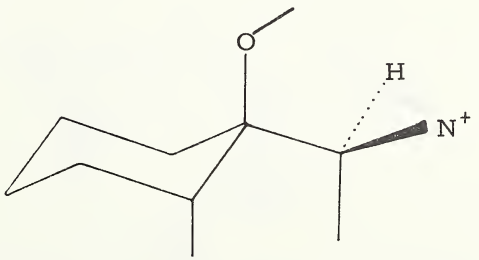


44

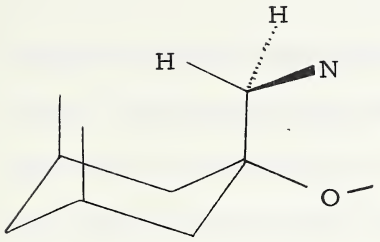
The interconversion of 42 (or 43) and the trans $^{+}$N/O form 44 will require higher energy than that involved for acetyl β-methylcholine 41, because the onium group in 44 is flanked by two bulky methyl substituents. It may be argued that the low potency of acetyl β,β-dimethylcholine compared to ACh and acetyl β-methylcholine is due in part at least to its difficulty in attaining trans $^{+}$N/O conformation. Similar considerations apply to the cyclohexyl ACh derivatives 14a-d. In both ax-acetate (45) and eq-acetate (46) gauche $^{+}$N/O conformations are preferred to trans. It is small wonder that cyclohexyl analogs



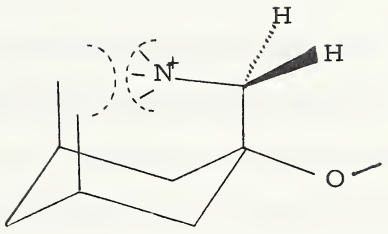
trans 45



gauche 45



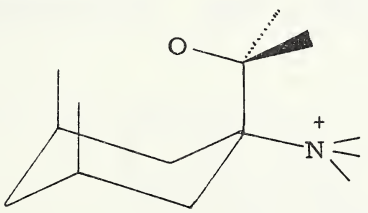
gauche 46



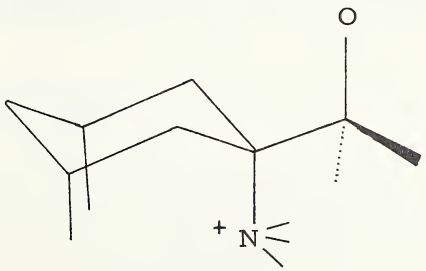
trans 46

14a-d are either inactive or feebly active as muscarinic agents because these analogs require higher energy to attain a trans $^{+}$N/O conformation.

It was then considered that perhaps the α,α-disubstituted analog 21 could exist in trans $^{+}$N/O conformation with less non-bonded interactions and should be more active as a muscarinic agent if other factors are not taken into consideration. It may be noted that in the two conformers of 21, namely, 47 and 48, the former is the more



47 (more stable form)

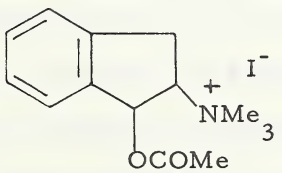


48

energetically favored isomer as the bulky trimethylammonium group is placed equatorially. Therefore, the major conformer of 21 is 47. If comparison is made between 47 and trans 46, one would presume

that 47 is a more stable form as the non-bonded interactions are smaller with acetate than with trimethylammonium whose size is equivalent to a t-butyl group. However, the pharmacological results (see Table 3) indicate that the α,α-disubstituted 21 is not more active than the β,β-disubstituted analogs. No satisfactory explanation can be attached to this observation. Perhaps the bulky cyclohexyl group opposes a close association of the molecule to the receptor site, and this bulky group is associated equally with both α,α and β,β-disubstituted analogs. The influence of this bulky group is so great that no difference in activity between α,α and β,β analogs could be found despite the existence of conformational preference.

It has been mentioned earlier that trans ACTM (8a) is as active as ACh at muscarinic receptors. We consider that a molecule, whose O/N^+ moiety can be held rigidly in a near trans conformation such as ACTM (8a), would serve as an interesting model to the present study. Thus, compounds 26 and 30 were made and tested.



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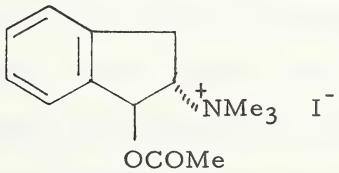

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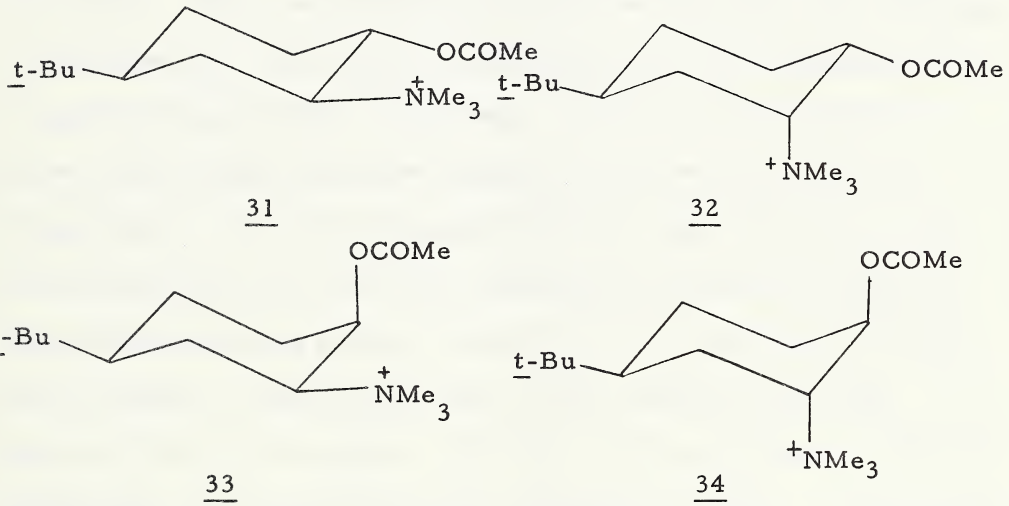
The pharmacological results (see Table 3) are discouraging. These two compounds are not active up to 10 mg/ml. It may be that the aromatic ring impedes the approach of the molecule to the receptor site and thus renders the compounds totally inactive. The same idea,

in which structurally rigid ACh analogs would serve as a good model to study the muscarinic receptors, led to the synthesis and evaluation of t-butylcyclohexyl ACh analogs 31, 32, 33 and 34. The chemical synthesis has been described elsewhere (Casy et al., 1972). It is of interest to note that among the four diastereomers, only 34 demonstrated weak activity, being 1.2×10^{-5} as active as ACh. This weak,

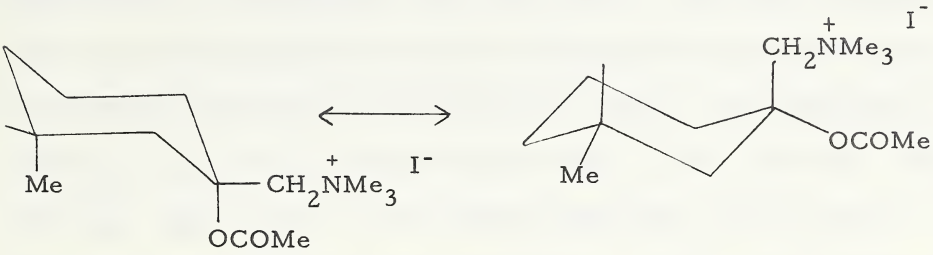


31 32 33 34

but significant activity of 34 confirms the earlier studies of Smissman et al. (1966), and Kay and Robinson (1970). These authors used decalin and cyclohexane respectively as the ring skeletons for ACh analogs, and found that trans or near trans $^{+}$N/O conformation of ACh active at the muscarinic receptor. All of these compounds are only weakly active.

It is of interest to note that 1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (c-Me-14c) possesses

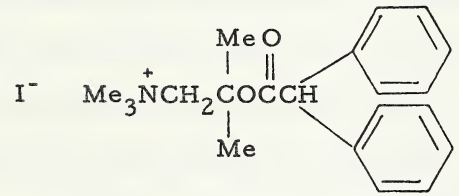
feeble activity whilst the corresponding desmethyl 14a and t-Me-14c



inverted conformer of c-Me-14c c-Me-14c

are inactive. This result indicates that the receptor site for c-Me-14c is stereospecific. The favored conformation of c-Me-14d appears to be ax-$CH_2{}^+N$, eq-OCOMe and eq-Me. As the inverted conformer has two bulky groups orientated axially it should be less stable conformationally. Since the desmethyl derivative 14a is inactive, it is proposed that the role of the 3-Me substituent could then be that of a conformational holding group so placed that it does not impede binding to the receptor. Alternatively, the 3-methyl group of c-Me-14c might contribute to the affinity of the molecule by providing an additional binding site, or by an allosteric effect upon the receptor. To clarify this problem, the optical isomeric pair of c-Me-14c was resolved and the difference in activity between the enantiomers compared. It is of great interest to note that (+)-c-Me-14c was found to be twice as active as the racemic mixture, (+)-c-Me-14c whilst the levo-isomer, (-)-c-Me-14c, was found to be totally inactive (see Table 3). Like our compounds, (+)-acetyl-β-methylcholine (41) is twice as active as the racemic mixture, whereas the levo isomer is weakly active as muscarinic agent (Beckett et al., 1963).

None of the compounds had any spasmogenic activity on the frog rectus in concentrations up to 100 μg/ml. This was a result which was not unexpected because β-methylation is known to reduce the nicotinic properties of ACh (Simonart, 1932). All compounds except 21, 26, and 30, antagonized the effect of ACh (Table 3). They were $\frac{2}{100}$ - $\frac{5}{100}$ as active as gallamine triethiodide, and no great difference in potency was found among them. Since these compounds were found to cause a parallel shift of the dose-response curve to ACh on the frog rectus preparation, they are classified as competitive antagonist of ACh. It is worth noting that their antagonistic effects are insensitive to configurational change. In view of the feeble antagonistic effect possessed by most of these compounds, we decided to make some benzilate and diphenyl acetate analogs of ACh (38) and (40). Benzilates and diphenylacetates were known to possess potent ACh antagonistic activity (Biel et al., 1962; Burtner and Cusic, 1943)



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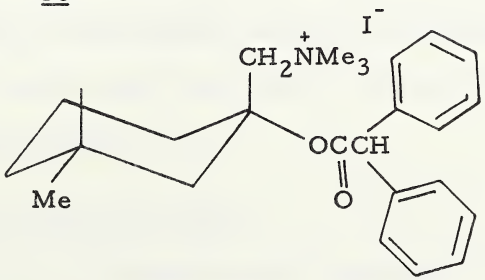

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at muscarinic receptors. The attempted synthesis of the benzilates met no success. However, diphenylacetates 38 and 40 were success fully made and their ACh antagonistic effect on the frog rectus evaluated. It was found that compounds 38 (2 μg/ml) and 40 (0.5 μg/ml) had a marked antagonistic effect on ACh. Since they were non-competitive antagonists, their potency could not be compared to that of the other competitive antagonists such as gallamine triethiodide.

Mechanism of Action of (+)-1-(N,N-Dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane Methiodide, (+)-c-Me-14c

Agents, which are known to induce the release of ACh, such as nicotine, carbachol, choline and tetramethylammonium (TMA), are not uncommon (Chiou and Long, 1969), but the stereoselectivity of these compounds has not been well investigated. During the course of determining muscarinic activity of all ACh analogs, it was observed that (+)-c-Me-14c or (±)-c-Me-14c induced a spasm on the guinea-pig ileum, the former being twice as active as the latter (see Table 3). We then considered the possibility that (+)-c-Me-14c was acting indirectly by a mechanism involving the release of ACh. Since a high stereospecificity was demonstrated for the agonistic activity of (+)-c-Me-14c, we felt that it would justify further examination of the effect of (+)-c-Me-14c. To this end, the following experiments were carried out and results were given.

(1) The Effect of Hyoscine Hydrobromide

The effect of hyoscine was studied on the responses to ACh,

(+)-c-Me-14c or DMPP. It was found that hyoscine in 0.01 μg/ml abolished responses to all three agonists.

(2) The Effect of Chlorpheniramine Maleate

Chlorpheniramine maleate, an antihistaminic drug, had little effect on the responses to ACh, (+)-c-Me-14c or DMPP.

(3) The Effect of Ganglionic Blocking Agents

The responses to ACh and (+)-c-Me-14c were not blocked by pentolinium tartrate 25 μg/ml or hexamethonium 25 μg/ml. However, responses to DMPP and nicotine were abolished by or reduced by these two ganglionic blocking agents.

(4) The Effect of Desensitization to Nicotine

The preparations were treated with Kreb's solution containing nicotine 20 μg/ml. This treatment abolished the responses of the tissue to DMPP and nicotine, but failed to block the response to either the compound or ACh.

(5) The Effect of Desensitization to Serotonin

Serotonin, 100 μg/ml failed to reduce the effect of ACh, (+)-c-Me-14c or DMPP. Responses to serotonin were abolished by this treatment.

(6) The Effect of Desensitization to DMPP

The effect of ACh on the preparation was slightly reduced as judged by a shift of the dose-response line, but the responses to both

DMPP and (+)-c-Me-14c were completely abolished.

(7) The Effect of Local Anesthetics

Both procaine hydrochloride (25 μg/ml) and lidocaine hydrochloride (10 μg/ml) selectively reduced the responses to (+)-c-Me-14c and DMPP more than they reduced the response to ACh.

(8) The Effect of Morphine

Morphine 10-50 μg/ml reduced the responses to (+)-c-Me-14c and DMPP but not ACh.

(9) The Effect of Tetrodotoxin

Tetrodotoxin 0.1 μg/ml abolished the response to c-Me-14c and DMPP without affecting the responses to ACh.

(10) The Effect of Cooling

Cooling the preparation to 25° or to 18° failed to block the response to either ACh or (+)-c-Me-14c. However, the response to DMPP was markedly reduced by both treatments.

(11) Denervation Studies

Several attempts were made to denervate the guinea-pig ileum using the method of Chiou and Long (1969); however, we were unable to reproduce their experiments and all the attempts failed.

(12) The Effect of Ouabain

It was hoped that ouabain could selectively block the nervous tissue without affecting the muscle in concentrations 1-100 μg/ml.

Unfortunately, we were unable to find a concentration of ouabain which could block the response to DMPP but not to ACh.

The effect of various agents on ACh and the test compound is shown in Figure 1. The possibilities of involvement of histamine or serotonin receptors are ruled out as the responses to the compound are not abolished by antihistaminics, such as chlorpheniramine maleate, or serotonin desensitization. It has been demonstrated that (+)-c-Me-14c does not interact with ganglia because it is not affected by ganglionic blocking agents such as hexamethonium chloride and pentolinium tartrate. It is also known that the compound does not act on the same receptor as nicotine at ganglia because responses to the compound were not abolished when the ganglia were desensitized by by the use of large doses of nicotine. It is of interest to note that a desensitizing dose of DMPP greatly reduced the responses to the compound without affecting the responses to ACh. These results are extremely interesting because they indicate that DMPP may be acting at a different site from that of nicotine at autonomic ganglia. An alternative explanation is that DMPP by causing persistent depolarization, depletes the stores of ACh at the nervous site involved in this particular case and hence is able to block the effect of the compound. The effect of the compound was blocked by tetrodotoxin; this result indicates that (+)-c-Me-14c does not act directly on muscarinic receptors and perhaps that its effect is of nervous origin. The effect of tetrodotoxin has been well reviewed (Russell, 1971). Tetrodotoxin

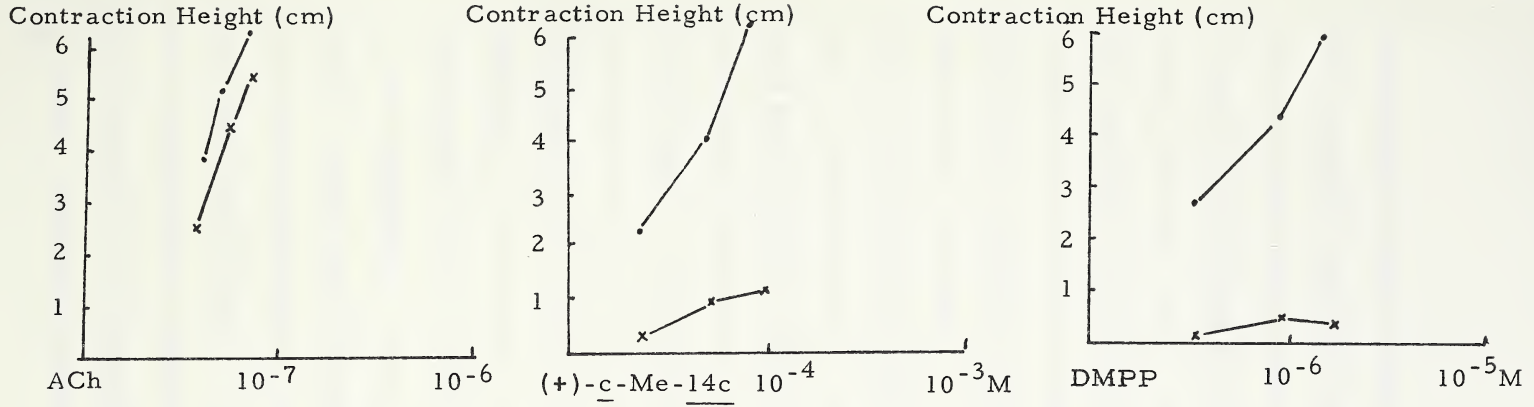


Figure 1a Log Dose-response Lines of ACh, (+)-c-Me-14c and DMPP (control —·—·—·—, in the presence of tetrodotoxin 3.5×10^{-7}M ——×——×——×). (Abcissa - log scale).

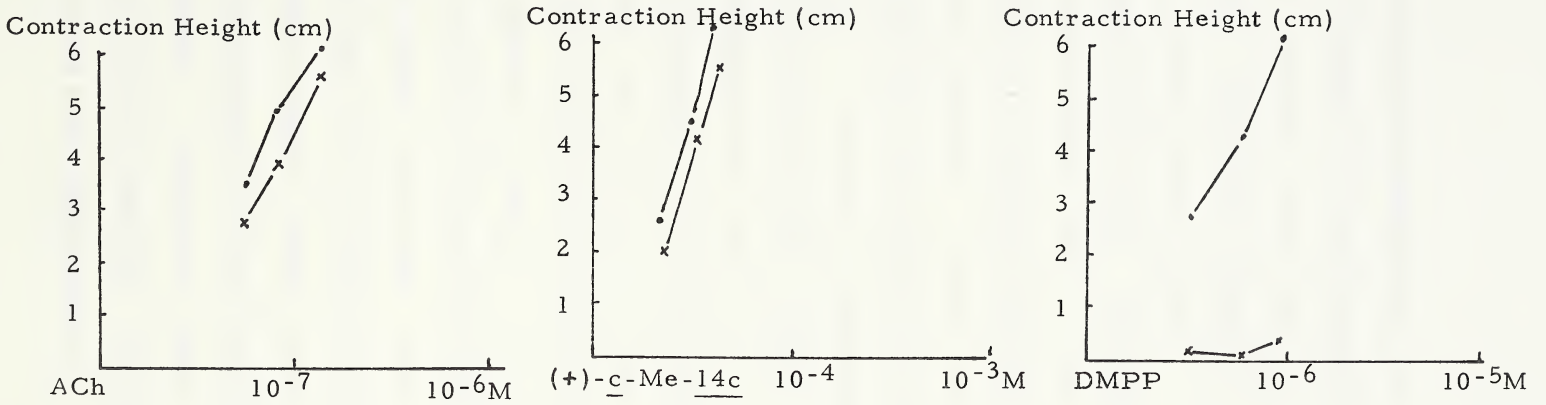


Figure 1b Log Dose-response Lines of ACh, (+)-c-Me-14c and DMPP (control —·—·—, in the presence of pentolinium 5×10^{-5}M ——×——×——×). (Abcissa - log scale).

prevents the increase in the early transient ionic permeability of the nerve normally associated with influx of sodium ion during excitation. It has no direct effect on the muscarinic receptor, as the responses to ACh are not affected by this treatment. It was then considered that (+)-c-Me-14c may act indirectly by causing release of ACh. Thus, morphine (10-50 μg/ml) was chosen for this study. Morphine is known for its ability to inhibit ACh release (Paton, 1957). It was found that the responses to the compound were reduced by treatment with morphine while those to ACh were not affected. It seems reasonable to assume that the effect of (+)-c-Me-14c on the guinea-pig ileum is due, at least in part, to ACh release. To secure a confirmative result that the effect of the compound is of nervous origin, cooling, denervation and blockade with local anesthetics were used in the present study. It was found that local anesthetics, such as lidocaine hydrochloride and procaine hydrochloride, reduced responses to the compound but not to ACh. It is generally accepted that the action of local anesthetics is the blockade of nerve conduction resulting in a reduction of ACh release. Since the effect of the compound is partially abolished by local anesthetics, this supports the previous conclusions. Unfortunately cooling and denervation studies were not successful and therefore positive proof that this compound acts through a nervous mechanism could not be found. It would be worthwhile to further the studies on the mechanism of action of this compound. One point we wish to stress specially is the stereospecificity of (+)-c-3-Me-14c. It is the cis isomer of the diastereomeric pair and it is the dextro isomer of

the enantiomers which demonstrates ACh releasing effect.

Melting points were determined on a Thomas Hoover capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Infrared Spectrophotometer Model 10-A. PMR spectra were determined on a Varian A-60D, HA-100 or HR-200 Spectrophotometer and chemical shifts are recorded in ppm (δ) downfield from tetramethylsilane (TMS). All samples were prepared by dissolving the samples (ca. 50 mg) in 0.5 ml of appropriate solvents. Mass spectra were run on AEI MS-9 Spectrophotometer using direct insertion probe. Elemental analyses were determined by the micro-analytical laboratories of the Faculty of Pharmacy and Pharmaceutical Sciences or by the Department of Chemistry, University of Alberta. Commercial chemicals were used without further purification unless otherwise specified.

EXPERIMENTAL

SYNTHESIS OF ACETYLCHOLINE ANALOGS AND THEIR PRECURSORS

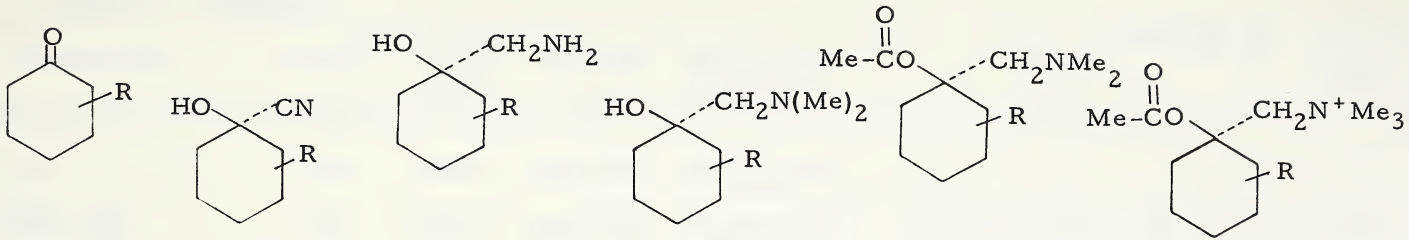
Most of acetylcholine analogs and their precursors were prepared by the general procedures I-V. Physical constants and elemental analyses are compiled in Table 4, and PMR data in Table 5. Analogs which were prepared by different methods are described elsewhere.

I. General Procedures for the Synthesis of Cyanohydrins (See Tables 4 and 5)

The preparation of 1-cyano-c,t-2-methyl-r-1-cyclohexanol (c,t-Me-10b) is typical.

A solution of 2-methylcyclohexanone (22.4 g, 0.2 mol) in methanol (50 ml) was added dropwise to a stirred solution of potassium cyanide (16 g, 0.24 mol) in water while the reaction mixture was kept at -2 to -5° by external cooling with dry ice and acetone. The reaction mixture was stirred at the same temperature for 2 hr after completion of the addition, and then made acidic with dilute hydrochloric acid. The reaction mixture was allowed to rise to room temperature and the organic layer separated. The aqueous layer was concentrated and extracted with ether (3 x 200 ml). The ether extracts and organic layer were combined and dried (Na_2SO_4). Removal of the solvent afforded the title compound which was purified by vacuum distillation.

Fractional crystallization of c,t-Me-10b (21.5 g) from a mixture of hexanes (b.p. 66-68°) gave pure 1-cyano-t-2-methyl-r-1-cyclohexanol (t-Me-10b) 13.6 g). Evaporation of the mother liquor



9 10 11 12 13 14

a, R = H b, R = 2-Me c, R = 3-Me d, R = 4-Me

Table 4 Elemental Analyses and Physical Properties etc. of Cyclohexyl ACh Analogs and Their Precursors

Compound[a]	Yield[b]	n_D^{20}	mp/bp[c]	Molecular formula	Analyses % Calcd. C	H	N	Found C	H	N
10a[d]	88	1.4942	80-84/2	$C_7H_{11}NO$						
c,t-Me-10b[e]	77	1.4660	72/0.05	$C_8H_{13}NO$						
t-Me-10b[e]	--	--	54-56	$C_8H_{13}NO$						
c,t-Me-10c[f]	85	1.4589	74-76/0.05	$C_8H_{13}NO$						
(-)-c,t-Me-10c	92	--	85-87/0.25	$C_8H_{13}NO$						
c,t-Me-10d	88	1.4622	78-80/0.25	$C_8H_{13}NO$						

Continued . . .

Table 4 - Continued

Compound[a]	Yield[b]	n_D^{20}	mp/bp[c]	Molecular formula	Analyses % Calcd. C	H	N	Found C	H	N
11a	78	1.4942	32/0.01	$C_7H_{15}NO$						
t-Me-11b	74	1.4839	60/0.05	$C_8H_{17}NO$	67.08	11.97	9.78	67.17	11.96	9.79
t-Me-11b HCl	89	--	212-215	$C_8H_{18}ClNO$	53.47	10.09		53.43	10.05	
c,t-Me-11b	70	1.4856	58-62/0.05	$C_8H_{17}NO$	67.08	11.97		67.04	11.67	
c,t-Me-11b HCl	90	--	208-210	$C_8H_{18}ClNO$	53.47	10.09		53.48	9.88	
c,t-Me-11c	79	1.4827	68-70/0.15	$C_8H_{17}NO$	67.08	11.97		67.44	11.97	
c,t-Me-11c HCl	81	--	171-179	$C_8H_{18}ClNO$	-	-		-	-	
c-Me-11c HCl	53	--	185-187	$C_8H_{18}ClNO$	53.47	10.09		53.56	9.88	
(+)-c-Me-11c HCl	76	--	188-189	$C_8H_{18}ClNO$	-	-		-	-	
(-)-c-Me-11c	41	--	-	$C_8H_{18}ClNO$	-	-		-	-	
c,t-Me-11d	81	1.4770	53-55/0.15	$C_8H_{17}NO$	67.08	11.97	9.78	67.07	12.08	9.76
12a	78	1.4645	34-36/0.07	$C_9H_{19}NO$	68.74	12.18		68.65	12.20	
12a HCl	92	--	172-174	$C_9H_{20}ClNO$	55.80	10.41	7.23	55.62	10.33	7.40
t-Me-12b	92	1.4625	56/0.075	$C_{10}H_{21}NO$	70.12	12.36		70.46	12.15	
t-Me-12bHCl	88	--	138-140	$C_{10}H_{22}ClNO$	57.82	10.68		58.19	10.39	

Continued . . .

Table 4 - Continued

Compound[a]	Yield[b]	n_D^{20}	mp/bp[c]	Molecular formula	Analyses % Calcd. C	H	N	Found C	H	N
c,t-Me-12b HCl	85	--	160-172	$C_{10}H_{22}ClNO$	57.82	10.68	-	57.56	10.57	-
c-Me-12b	26	--	188-190	$C_{10}H_{22}ClNO$	57.82	10.68	7.23	57.56	10.57	7.41
c-Me-12c	59	1.4603	95-96/24	$C_{10}H_{22}NO$	70.12	12.36	8.12	70.16	12.59	8.08
c-Me-12c HCl	99	--	173-175	$C_{10}H_{22}ClNO$	57.82	10.68	6.74	57.83	10.63	7.11
(+)-c-Me-12c HCl	79	--	173-175	$C_{10}H_{22}ClNO$	-	-	-	-	-	-
(-)-c-Me-12c HCl	81	--	169-170	$C_{10}H_{22}ClNO$	57.82	10.68	6.74	-	-	-
c,t-Me-12c HCl	82	--	145-150	$C_{10}H_{22}ClNO$	57.82	10.68	-	57.70	10.58	-
c,t-Me-12d HCl	91	--	157-160	$C_{10}H_{22}ClNO$	-	-	-	-	-	-
t-Me-12d HCl	49	--	174-175	$C_{10}H_{22}ClNO$	57.82	10.68	6.74	57.81	10.50	6.52
13a HCl	80	--	175-176	$C_{11}H_{22}ClNO_2$	56.04	9.40	-	-	-	-
t-Me-13b HCl	74	--	188-190	$C_{12}H_{24}ClNO_2$	57.70	9.69	-	-	-	-
c-Me-13b HCl	85	--	194-195	$C_{12}H_{24}ClNO_2$	57.70	9.69	-	-	-	-
c,t-Me-13c HCl	84	--	202-204	$C_{12}H_{24}ClNO_2$	-	-	-	-	-	-
(+)-c-Me-13c HCl	97	--	216-217	$C_{12}H_{24}ClNO_2$	57.70	9.69	-	-	-	-
(-)-c-Me-13c HCl	81	--	217-218	$C_{12}H_{24}ClNO_2$	57.70	9.69	-	-	-	-

Continued . . .

Table 4 - Continued

Compounds	Yield	n_D^{20}	mp/bp[c]	Molecular formula	Analyses % Calcd. C	H	N	Found C	H	N
t-Me-13c HCl	26	-	205-206	$C_{12}H_{24}ClNO_2$	57.70	9.69		58.60	9.90	
c-Me-13c HCl	89	-	208-209	$C_{12}H_{24}ClNO_2$	57.70	9.69	5.61	57.82	9.63	5.88
c,t-Me-13d HCl	97	-	194-196	$C_{12}H_{24}ClNO_2$	57.70	9.69		58.10	9.40	
t-Me-13d HCl	82	-	189-191	$C_{12}H_{24}ClNO_2$						
15	68	-	132-134	$C_8H_{18}ClNO_2 \cdot \frac{1}{2}H_2O$	49.88	8.84		49.76	8.99	
14a	44	-	156-158	$C_{12}H_{24}INO_2$	42.24	7.09		42.58	7.16	
t-Me-14b	77	-	149-151	$C_{13}H_{26}INO_2$	43.95	7.38		43.92	7.20	
c-Me-14b	62	-	145-147	$C_{13}H_{26}INO_2$	43.95	7.38		43.86	7.28	
t-Me-14c	79	-	106-108	$C_{13}H_{26}INO_2$	43.95	7.38		44.40	7.40	
c-Me-14c	52	-	150-151	$C_{13}H_{26}INO_2$	43.95	7.38		44.15	7.52	
(+)-c-Me-14c	65	-	158-160	$C_{13}H_{26}INO_2$	43.95	7.38	3.96	43.61	7.44	3.69
(-)-c-Me-14c	90	-	152-154	$C_{13}H_{26}INO_2$	43.95	7.38		43.82	7.55	
t-Me-14d	86	-	137-139	$C_{13}H_{26}INO_2$	43.95	7.38		44.25	7.47	
c-Me-14d	62	-	179-181	$C_{13}H_{26}INO_2$	43.95	7.38	3.96	43.65	7.03	3.76
16[h]	89	-	185-189	$C_9H_{20}INO_2$	35.89	6.69		36.10	6.62	

Footnotes to Table 4

a with reference to OH or OCOMe

b based on immediate precursor

c in ^{o}C, pressure (where appropriate) in mm Hg

d Barbulescu and Stoica, 1964, reported n_D^{20} 1.4940, b.p. 73°/0.5

e Kamernitskii and Akhrem, 1959, reported n_D^{20} 1.4670, b.p. 95-96/0.4

f Akhrem and Kamernitskii, 1959, gave n_D^{20} 1.4620

g Tchoubar, 1949, gave n_D^{18} 1.460, Chem. Abstr., 44, 4431 g reported, n_D^{18} 1.4600

h Cocolas et al., 1970, give m.p. 185-186°

Table 5 Proton Magnetic Resonance Characteristics of Cyclohexyl ACh Analogs 10-14

No.	Compound[a]	Solvent	Proton group	Chemical shift[b]
1	c,t-Me-10b	DMSO-d_6	OH	6.31*, 6.10
	t-Me-10b	DMSO-d_6	OH	6.31
2	c,t-Me-10c	DMSO-d_6	OH	6.45*, 6.15
3	c,t-Me-10d	DMSO-d_6	OH	6.40*, 6.13
4	c,t-Me-11c HCl	DMSO-d_6	OH	5.13, 4.77*
	c-Me-11c HCl	DMSO-d_6	OH	5.13
5	c,t-Me-12b HCl	DMSO-d_6	OH	5.08, 4.77*
	t-Me-12b HCl	DMSO-d_6	OH	5.08
	c-Me-12b HCl	DMSO-d_6	OH	4.77
6	c,t-Me-12d HCl	D_2O	CH_2N	3.33*, 3.19
	t-Me-12d HCl	D_2O	CH_2N	3.33
7	c,t-Me-13c HCl	$CDCl_3$	OCOMe	2.12*, 2.08
	c-Me-13c HCl	$CDCl_3$	OCOMe	2.08
	(-)-c-Me-13c HCl	$CDCl_3$	OCOMe	2.09
	t-Me-13c HCl	$CDCl_3$	OCOMe	2.12
8	c-Me-14d	D_2O	4-Me	0.87 (doublet)
			OCOMe	2.15
			NMe_3	3.23
			CH_2N	3.93

Continued . . .

Table 5 - Continued

No.	Compound[a]	Solvent	Proton group	Chemical shift[b]
8	t-Me-14d	D_2O	4-Me	0.93 (doublet)
			OCOMe	2.12
			NMe_3	3.28
			CH_2N	3.98
9	c-Me-14c	$CDCl_3$	OCOMe	2.08
			NMe_3	3.65
			CH_2N	4.40
	t-Me-14c	$CDCl_3$	OCOMe	2.12
			NMe_3	3.57
			CH_2N	4.33
	(-)-c-Me-14c	D_2O	OCOMe	2.10
			NMe_3	3.32
			CH_2N	4.03
10	14a	D_2O	OCOMe	2.15
			NMe_3	3.27
			CH_2N	3.93
		$CDCl_3$	OCOMe	2.13
			NMe_3	3.59
			CH_2N	4.39

[a] with reference to OH or OCOMe

[b] in ppm from TMS (δ); signals are singlets unless otherwise stated, major signal of mixtures carries asterisk.

from t-Me-10b gave a cis-enriched isomeric mixture which was used in a subsequent synthesis.

Similarly prepared were:

cyclohexanone cyanohydrin (10a) from cyclohexanone (9a);

a mixture of 1-cyano-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-10c) from 3-methylcyclohexanone;

a mixture of (-)-1-cyano-c,t-3-methyl-r-1-cyclohexanol (-)-(c,t-Me-10c) from (+)-3-methylcyclohexanone; $[\alpha]_D^{25}$ -7.6° (c 10, EtOH);

a mixture of 1-cyano-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-10d) from 4-methylcyclohexanone.

Recrystallization of c,t-Me-10c and c,t-Me-10d from various solvents failed to separate the component configurational isomers.

The IR spectra of all the compounds displayed hydroxyl absorption bands at 3500-3200 cm^{-1} and nitrile absorption bands at 2300-2200 cm^{-1}.

II. General Procedure for the Preparation of Amino-alcohols and Their Hydrochloride Salts (See Tables 4 and 5)

The preparation of 1-(aminomethyl)cyclohexanol (11a) is typical.

Lithium aluminum hydride (20 g, 0.55 mol) was suspended in anhydrous ether (800 ml). An ethereal solution (200 ml) of cyclohexanone cyanohydrin (40 g, 0.32 mol) was added dropwise to the suspension. When the addition was complete, the reaction mixture was heated under reflux for 10 hr, and allowed to cool. The excess lithium aluminum hydride was decomposed by careful addition of water

(50 ml) and 20% sodium hydroxide solution (100 ml). The ethereal solution was decanted and dried over anhydrous sodium sulfate. Removal of the solvent gave the product as an oily residue (36 g).

Using essentially the same method the following compounds were prepared:

1-aminomethyl-t-2-methyl-r-1-cyclohexanol (t-Me-11b) and its hydrochloride from 1-cyano-t-2-methyl-r-1-cyclohexanol (t-Me-10b);

1-aminomethyl-c,t-2-methyl-r-1-cyclohexanol (c,t-Me-11b) and its hydrochloride from 1-cyano-c,t-2-methyl-r-1-cyclohexanol (c,t-Me-10b);

1-aminomethyl-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-11c) and its hydrochloride from 1-cyano-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-10c);

(+)-1-aminomethyl-c,t-3-methyl-r-1-cyclohexanol hydrochloride (c,t-Me-11c HCl) from (-)-1-cyano-c,t-3-methyl-r-1-cyclohexanol (-)-(c,t-Me-10c)

1-aminomethyl-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-11d) from 1-cyano-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-10d).

The hydrochlorides of these amines were made by adding ethereal hydrogen chloride to a solution of each amine in the same solvent and were recrystallized from absolute ethanol and ether. The hydrochloride of c,t-Me-11d was very hygroscopic and not characterized.

Repeated crystallization of the hydrochloride of c,t-Me-11c (45 g) from ethanol and ether gave pure 1-aminomethyl-c-3-methyl-r-

1-cyclohexanol hydrochloride (c-Me-11c HCl) (20 g). By a similar operation, (+)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol hydrochloride (+)-(c-Me-11c HCl, 6 g) was isolated from the cis and trans mixture (24 g); the free base had $[\alpha]^{25^\circ}_{260nm}$ 13° (c 0.4, H_2O). (-)-1-Aminomethyl-c-3-methyl-r-1-cyclohexanol ((-)-(c-Me-11c)) was prepared in the following manner. A mixture of (+)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol (29.6 g, 0.2 mol) and d-tartaric acid (31 g, 0.2 mol) in acetone (400 ml) and absolute ethanol (80 ml) was heated under reflux for 2 hr. After cooling, the solution was filtered and allowed to stand for 5 days. The diastereoisomeric salt (29 g) was collected and recrystallized five times from a mixture of acetone and absolute ethanol. The specific rotation of the product (12 g) was found to be constant. The salt was then treated with 20% sodium hydroxide solution and the free base extracted into ether (3 x 50 ml). Removal of the solvent afforded the title compound (5 g), $[\alpha]^{25^\circ}_{260\ nm}$ -12.5 (c 0.4, H_2O).

IR spectra of all the amino-alcohol hydrochlorides displayed hydroxyl absorption bands near 3400-3300 cm^{-1} and isolated NH_3 bands near 2000 cm^{-1} typical of primary amino-alcohol hydrochlorides (Thompson et al., 1965).

III. General Procedure for the Synthesis of N,N-Dimethyl-amino-alcohols and Their Hydrochloride Salts (See Tables 4 and 5)

The preparation of 1-(N,N-dimethylaminomethyl)-cyclohexanol (12a) is typical.

A mixture of 1-(aminomethyl)cyclohexanol (3.9 g, 0.03 mol), 37% formaldehyde solution (5 ml, 0.06 mol), 90% formic acid (4.5 g, 0.06 mol) and water (6 ml) was heated under reflux for 6 hr. After cooling, the reaction mixture was made basic with 20% sodium hydroxide solution and extracted with ether (3 x 20 ml). The combined ethereal extracts were dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was distilled under reduced pressure. The hydrochloride salt 12a HCl was made as described in Procedure II.

The following compounds were prepared in a similar manner:

1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-cyclohexanol (t-Me-12b) and its hydrochloride from 1-aminomethyl-t-2-methyl-r-1-cyclohexanol (t-Me-11b);

1-(N,N-dimethylaminomethyl)-c,t-2-methyl-r-1-cyclohexanol hydrochloride (c,t-Me-12b HCl) from 1-aminomethyl-c,t-2-methyl-r-1-cyclohexanol (c,t-Me-11b);

1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol (c-Me-12c) and its hydrochloride from 1-aminomethyl-c-3-methyl-r-1-cyclohexanol (c-Me-11c);

1-(N,N-dimethylaminomethyl)-c,t-3-methyl-r-1-cyclohexanol hydrochloride (c,t-Me-12c HCl) from 1-aminomethyl-c,t-3-methyl-r-1-cyclohexanol (c,t-Me-11c);

(+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol hydrochloride ((+)-(c-Me-12c HCl)) $[\alpha]_{260\ nm}^{25^\circ}$ +7.5 (c, 0.4, H_2O)

from (+)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol (+)-(c-Me-11c); (-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol hydrochloride (+)-(c-Me-12c HCl) $[\alpha]^{25}_{260nm}$ -7.5 (c 0.4, H_2O) from (-)-1-aminomethyl-c-3-methyl-r-1-cyclohexanol (-)-(c-Me-11c); 1-(N,N-dimethylaminomethyl)c,t-4-methyl-r-1-cyclohexanol (c,t-Me-12d) from 1-aminomethyl-c,t-4-methyl-r-1-cyclohexanol (c,t-Me-11d).

Fractional crystallization of cis-enriched c,t-Me-12b HCl (3.8 g) from absolute ethanol and ether gave pure 1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-cyclohexanol hydrochloride (c-Me-12b HCl) (1.0 g).

Repeated crystallization of c,t-Me-12d HCl (27.5 g) from absolute ethanol and ether afforded pure 1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-cyclohexanol hydrochloride (t-Me-12d HCl) (13.5 g); the mother liquor was concentrated and the trans-enriched c,t-Me-12d HCl used in a subsequent synthesis.

The IR spectra of all the tertiary amino-alcohol hydrochlorides showed hydroxyl abosrption bands at 3400-3300 cm^{-1} and several bands near 2500 cm^{-1} (N^+HMe_2).

IV. General Procedure for the Synthesis of Amino-ester Hydrochlorides (See also Table 4 and 5)

The preparation of 1-(N,N-dimethylaminomethyl)-cyclohexyl acetate hydrochloride (13a) is typical.

1-(N,N-Dimethylaminomethyl)cyclohexanol (4.8 g, 0.03 mol) was dissolved in ethyl acetate (60 ml). This solution was chilled in

an ice bath, and to it was added, with vigorous stirring, a solution of acetyl chloride (4.9 g, 0.05 mol) in ethyl acetate (10 ml). The reaction mixture was heated under reflux for 6 hr and allowed to cool. The resulting precipitate was collected and recrystallized from a mixture of absolute ethanol and ether.

The following compounds were prepared in a similar manner:

1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-acetoxycyclohexane hydrochloride (c-Me-13b HCl) from 1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-cyclohexanol hydrochloride (c-Me-12b HCl);

1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-acetoxycyclohexane hydrochloride (t-Me-13b HCl) from 1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-cyclohexanol (t-Me-12b);

1-(N,N-dimethylaminomethyl)-c,t-3-methyl-r-1-acetoxycyclohexane hydrochloride (c,t-Me-13c HCl) from 1-(N,N-dimethylaminomethyl)-c,t-3-methyl-r-1-cyclohexanol hydrochloride (c,t-Me-12c HCl);

1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (c-Me-13c HCl) from 1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol (c-Me-12c);

(+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (+)-(c-Me-13c HCl) $[\alpha]^{25^\circ}_{260\ nm}$ +62.5 (c 0.4, H_2O) from (+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-cyclohexanol hydrochloride (+)-(c-Me-12c HCl)

(-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (-)-(c-Me-13c HCl) $[\alpha]^{25^\circ}_{260\ nm}$ -50 (c 0.4, H_2O) from (-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-

cyclohexanol hydrochloride (-)-(c-Me-12c HCl)

1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-acetoxycyclohexane hydrochloride (c,t-Me-13d HCl) from 1-(N,N-dimethylaminomethyl)-c,t-4-methyl-r-1-cyclohexanol hydrochloride (c,t-Me-12d HCl);

1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-acetoxycyclohexane hydrochloride (t-Me-13d HCl) from 1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-cyclohexanol hydrochloride (t-Me-12d HCl).

Repeated crystallization of c,t-Me-13c HCl (3.0 g) from absolute ethanol and ether gave pure 1-(N,N-dimethylaminomethyl)-t-4-methyl-r-1-acetoxycyclohexane hydrochloride (t-Me-13c HCl).

1,1-Dimethyl-2-(N,N-dimethylamino)ethyl acetate hydrochloride (15) was prepared from 1-dimethylamino-2-methyl-2-propanol (Gresham, 1949).

IR spectra of all amino-esters displayed absorption bands near 2500 cm^{-1} ($N^{+}HMe_2$) and ester absorption bands near 1730 cm^{-1}.

V. General Procedure for the Synthesis of Amino-ester Methiodides (See also Table 4 and 5)

The preparation of 1-(N,N-dimethylaminomethyl)-cyclohexyl acetate methiodide (14a) is typical.

1-(N,N-Dimethylaminomethyl)cyclohexyl acetate hydrochloride (1.3 g, 0.006 mol) was dissolved in ice water (10 ml) and the solution was made basic with 5% sodium bicarbonate solution. The solution was extracted with ether (3 x 10 ml) and the combined ether extracts dried over anhydrous sodium sulfate. The solvent was evaporated

and the residue dissolved in a small amount of acetone (5 ml). Excess methyl iodide was added to the acetone solution. On standing, the methiodide precipitated and was recrystallized from absolute ethanol/ether.

The following compounds were prepared in a similar manner:

1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-acetoxycyclohexane methiodide (c-Me-14b) from 1-(N,N-dimethylaminomethyl)-c-2-methyl-r-1-acetoxycyclohexane hydrochloride (c-Me-13b HCl);

1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-acetoxycyclohexane methiodide (t-Me-14b) from 1-(N,N-dimethylaminomethyl)-t-2-methyl-r-1-acetoxycyclohexane hydrochloride (t-Me-13b HCl);

1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (c-Me-14c) from 1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (c-Me-13c HCl);

1-(N,N-dimethylaminomethyl)-t-3-methyl-r-1-acetoxycyclohexane methiodide (t-Me-14c) from 1-(N,N-dimethylaminomethyl)-t-3-methyl-r-1-acetoxycyclohexane hydrochloride (t-Me-13c HCl);

(+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (+)-(c-Me-14c) $[\alpha]^{25^\circ}_{260\ nm}$ +47.5° (c 0.4, H_2O) from (+)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (+)-(c-Me-13c);

(-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane methiodide (-)-(c-Me-14c) $[\alpha]^{25^\circ}_{260\ nm}$ -45° (c 0.4, H_2O) from (-)-1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-acetoxycyclohexane hydrochloride (-)-(c-Me-13c);

1-(*N*,*N*-dimethylaminomethyl)-*c*,*t*-4-methyl-*r*-1-acetoxycyclohexane methiodide (*c*,*t*-Me-14d) from 1-(*N*,*N*-dimethylaminomethyl)-*c*,*t*-methyl-*r*-1-acetoxycyclohexane hydrochloride (*c*,*t*-Me-13d HCl); 1-(*N*,*N*-dimethylaminomethyl)-*t*-4-methyl-*r*-1-acetoxycyclohexane methiodide (*t*-Me-14d) from 1-(*N*,*N*-dimethylaminomethyl)-*t*-4-methyl-*r*-1-acetoxycyclohexane hydrochloride (*t*-Me-13d HCl); acetyl-β,β-dimethylcholine iodide (16) from 1,1-dimethyl-2-(*N*,*N*-dimethylamino)ethyl acetate hydrochloride (15).

Fractional crystallization of *c*,*t*-Me-14d from absolute ethanol and ether gave pure 1-(*N*,*N*-dimethylaminomethyl)-*c*-4-methyl-*r*-1-acetoxycyclohexane methiodide (*c*-Me-14d).

The IR spectra of all the quaternary ammonium salt acetates exhibited ester absorption bands near 1740-1730 cm^{-1}.

(1-Nitrocyclohexyl)methanol (17)

37% Formalin (45 ml, 0.55 mol) was added to a mixture of nitrocyclohexane (24 g, 0.17 mol) and sodium hydroxide (1g) in ethanol (200 ml) over a period of 0.5 hr. During this time, the reaction mixture was stirred and maintained at about 55°. After a further 3 hr at this temperature, the solvent was removed and the residue was poured into dilute hydrochloric acid (150 ml). The organic layer was extracted with benzene (50 ml) and dried (Na_2SO_4). Removal of the solvent afforded the crude title compound which was purified by vacuum distillation to give 22 g (80%) of the product, b.p. 108-112°/0.15 mm, n_D^{20} 1.4855. (Wheatley, 1954, reported b.p.

110-114°/3 mm, n_D^{20} 1.4855).

IR (film);

ν_{max} 1530 and 1345 (NO_2) cm^{-1}.

(1-Aminocyclohexyl)methanol (18)

A solution of (1-nitrocyclohexyl)methanol (16 g, 0.1 mol) in dry ether (50 ml) was added dropwise to a suspension of lithium aluminum hydride (10 g, 0.25 mol) in the same solvent (300 ml) with stirring. The reaction mixture was further heated for 6 hr after completion of the addition. The excess lithium aluminum hydride was decomposed by careful addition of water (20 ml) and 20% aqueous sodium hydroxide (30 ml). The ethereal solution was decanted and the residue was extracted repeatedly with ether (5 x 50 ml). The combined ether extracts were dried (Na_2SO_4). The solution was concentrated and the residue was distilled in vacuo to give 7.5 g (58%) of the title compound, b.p. 98-100°/0.3 mm, n_D^{25} 1.4950. (Wheatley, 1954 reported b.p. 114-118°/14 mm, n_D^{25} 1.4964).

IR (film):

ν_{max} broad absorption band at 3500-3000 cm^{-1} (primary amino-alcohol).

PMR (DMSO-d_6):

δ5.12 (1H, t, J=4.7 Hz, OH), absent after deuteration.

(1-N,N-Dimethylaminocyclohexyl)methanol (19)

The title compound was prepared in 64% yield from (1-amino-cyclohexyl)-methanol by the procedure used for the synthesis of

N,N-dimethylamino-alcohols (12). The hydrochloride salt of the compound melted at 182-195° (from ethanol and ether). (Wheatley, 1954, gave 185-187°).

IR (film):

ν_{max} 3300 (H-bonded OH) cm^{-1}

(1-N,N-Dimethylaminocyclohexyl)methanol Methiodide (20)

A mixture of the tertiary amino-alcohol 19 (2.0 g, 0.013 mol) and methyl iodide (10 g) in acetone (20 ml) was stirred at room temperature for 4 hr. The amino-alcohol methiodide (20) precipitated out of the solution and was collected (2.2 g, 58%), m.p. 163-165° (from absolute ethanol and acetone), (Wheatley, 1954, reported 157-160°)

PMR (DMSO-d_6):

δ5.40 (1H, t, J=4.7 Hz, OH), absent after deuteration.

(1-N,N-Dimethylaminocyclohexyl)methyl Acetate Methiodide (21)

The alcohol 20 (2.2 g, 7 mmol) was stirred in acetic anhydride (10 ml) at room temperature for 24 hr. Excess of acetic anhydride was removed in vacuo and the residue was recrystallized from absolute ethanol and ether to give 1.1 g (48%) of the title compound, m.p. 163-164° (Wheatley, 1954, gave 167-169°).

IR (nujol mull):

ν_{max} 1740 (C=O) cm^{-1}

1-(N,N-Dimethylaminomethyl)cyclohexanol Methiodide (20a)

A mixture of 1-N,N-dimethylaminomethyl-1-cyclohexanol (12a) (8 g, 0.05 mol) and methyl iodide (21 g, 0.15 mol) in acetone (50 ml) was stirred at room temperature for 10 min. The title compound precipitated out of the solution and was collected, m.p. 203-205° (from methanol and acetone), yield 80%.

Anal. Calcd. for $C_{10}H_{22}INO$: C, 40.14; H, 7.41; N, 4.68.
Found: C, 40.06; H, 7.31; N, 4.70.

Attempted Synthesis of 1-(N,N-Dimethylaminomethyl)cyclohexyl Acetate Methiodide (14a) from (20a)

A mixture of 20a (9 g, 0.03 mol) and zinc chloride (0.5 g) in acetic anhydride was heated under reflux for 24 hr. Anhydrous ether was added dropwise to the cooled mixture until cloudiness appeared. The reaction mixture was placed in the refrigerator and the precipitate (3.2 g, 32%), m.p. 170-175° was collected. The precipitate showed an ester absorption band at 1740 cm^{-1} in its IR spectrum, and an N^+Me_3 signal at δ3.90 in its PMR spectrum, but did not give the required elemental analysis. Repeated recrystallization failed to improve the purity of this compound.

2-Hydroxyimino-1-indanone (22)

Ethyl nitrite was generated in the following manner. Solution I contained sodium nitrite (310 g, 4.5 mol), 95% ethanol (210 g, 2.3 mol), and water to make up 1.2 l. Solution II contained sulfuric acid (120 g, or 184 ml, sp. gr. 1.84), 95% ethanol (110 g) and water to make up 1.2 l.

Solution I was placed in a two necked flask. One neck was fitted tightly with a separatory funnel containing solution II, in the other a glass tube was inserted to deliver the generated ethyl nitrite. Ethyl nitrite could be generated continuously by addition of solution II to I. Ethyl nitrite was bubbled into a stirred solution of 1-indanone (24 g, 0.18 mol) and hydrochloric acid (20 ml) in ethanol (250 ml). After 5-10 min, the title compound formed and precipitated out of the solution; this was collected by filtration. The filtrate was further aerated with ethyl nitrite to form more product. A total of 24 g (86%) of the title cmpound was obtained, m.p. 200-206° (Huebner et al., 1962, reported 214-220°).

c-2-Amino-1-hydroxyindan (23)

A partial suspension of 2-hydroxyimino-1-indanone (7.5 g, 0.047 mol), palladium black (1.13 g) and conc. sulfuric acid (1.5 ml) in glacial acetic acid (29 ml) was shaken in a Parr hydrogenation apparatus at room temperature and 30-45 p.s.i. hydrogen pressure for 7 hr. At the end of the reaction, a large amount of the product as the amine sulfate precipitated out of solution. The reaction mixture was diluted with warm water (5-10 ml) to dissolve this salt and the catalyst filtered off. A molar equivalent of 20% sodium hydroxide solution was added to neutralize the sulfuric acid and the mixture was evaporated to a paste. The mixture was extracted with ethyl acetate (3 x 40 ml), and the extracts dried (Na_2SO_4). Evaporation of the solvent gave the title compound, which after one recrystallization from benzene melted at 102-104°, yield 4.0 g (58%), (Rosen

and Green, 1963, reported 105-109°).

IR (nujol mull):

ν_{max} 3350 and 3280 (amino-alcohol) cm^{-1}.

PMR (DMSO-d_6):

δ3.50 (1H, m, methine H_2), 4.73 (1H, d. J=5.4 Hz, H_1), and 7.23 (4H, br. s, aromatic).

c-2-Dimethylamino-1-hydroxyindan (24)

The title compound was prepared from c-2-amino-1-hydroxyindan in a manner similar to the one described for 1-(N,N-dimethylaminomethyl)cyclohexanol (12a) in a yield of 67%, m.p. 110-113° (from hexanes b.p. 66-68°), (Huebner, 1970, reported 124-126°).

IR (nujol mull):

No OH band above 3000 cm^{-1}.

PMR (DMSO-d_6):

δ2.28 (6H, s, NMe_2), 3.63 (1H, br. s, OH), 4.68 (1H, d, J=4.7 Hz, H_2), and 7.24 (4H, m, aromatic).

c-1-Acetoxy-2-dimethylaminoindan Hydrochloride (25)

The title compound was synthesized from c-2-dimethylamino-1-hydroxyindan (24) by a procedure similar to the one described for 1-(N,N-dimethylaminomethyl)cyclohexyl acetate hydrochloride (13a) in a yield of 70%, m.p. 180-182° (from dry ether and ethanol).

IR (nujol mull):

ν_{max} 2250 and 2442 (N^+H), 1745 (ester, C=O) cm^{-1}.

PMR (DMSO-d_6):

δ2.11 (3H, s, acyl Me), 2.93 (6H, s, NMe_2), 6.26 (1H, d, J=5.2 Hz, H_1), and 7.41 (4H, br. s, aromatic).

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48.
Found: C, 61.17; H, 7.18; N, 5.66.

c-1-Acetoxy-2-dimethylaminoindan Methiodide (26)

The title compound was prepared from c-1-acetoxy-2-dimethylaminoindan hydrochloride by the method described for 1-(N,N-dimethylaminomethyl)cyclohexyl acetate methiodide (14a) in a yield of 81%. One recrystallization from methanol gave a m.p. 230-232°.

IR (nujol mull):

ν_{max} 1745 (ester C=O), 1210 (ester C-O) cm^{-1}

PMR (DMSO-d_6):

δ2.28 (3H, s, acyl Me), 3.40 (9H, s, N^+Me_3), 4.53 (1H, br. s, H_2) and 6.37 (1H, d, J=4.7 Hz, H_1).

Anal. Calcd. for $C_{15}H_{20}INO_2$: C, 48.27; H, 5.40; N, 3.75.
Found: C, 47.93; H, 5.63; N, 3.63.

Alternate method for the preparation of c-1-acetoxy-2-dimethylaminoindane Methiodide (26)

A mixture of c-2-dimethylamino-1-hydroxyaminoindan (24) (1 g, 6 mmol) and acetic anhydride (10 ml) was stirred at room temperature for 7 days. The reaction mixture was then treated with excess methyl iodide, and stirred for another 3 hr. The title compound formed and precipitated out of the solution, yield 88%, m.p.

230-232° (from ethanol).

t-2-Amino-1-hydroxyindan (27) and its Hydrochloride

2-Hydroxyimino-1-indanone (22) (15 g, 0.094 mol) was dissolved in 5% aqueous sodium hydroxide solution and was added to ethanol (95%, 200 ml) containing 5% Pd/C (1.5 g). The reaction mixture was then hydrogenated at room temperature and atmospheric pressure. When hydrogen uptake stopped (7 l), the catalyst was filtered off and the solvent removed. The residue was taken up in chloroform (150 ml) and aerated with hydrogen chloride gas to give the title compound as a hydrochloride salt (8.1 g, 49%), m.p. 218-220° (Huebner et al., 1970, reported 222-224°).

The free base was prepared by dissolving the hydrochloride salt in a minimum amount of water, and basifying with 20% sodium hydroxide solution, followed by extraction with chloroform. Evaporation of the solvent afforded the crude free base, m.p.104-105° (Huebner et al., 1970, reported 100-103°).

IR (free base in nujol mull):

ν_{max} a sharp band at 3360 cm^{-1} and a broad band between 3400-3000 cm^{-1} characteristic of a primary amino-alcohol.

PMR (free base in DMSO-d_6):

δ4.64 (1H, d, J=5.8 Hz, H_1), and 7.23 (4H, m, aromatic).

t-2-Dimethylamino-1-hydroxyindan (28)

The title compound was prepared from t-2-amino-1-hydroxyindan in a manner similar to that described for c-2-dimethylamino-1-

hydroxyindan (23). The product was isolated in 77% yield, m.p. 104-105° (from ethanol and ether), (Huebner et al., 1970, reported 105-107°).

IR (nujol mull):

ν_{max} a broad band at 3400-3000 (OH) cm^{-1}.

PMR (DMSO-d_6):

δ2.28 (6H, s, NMe_2), 4.98 (1H, br. s, H_1), and 7.23 (4H, m, aromatic).

t-1-Acetoxy-2-dimethylaminoindan Hydrochloride (29)

The title compound was prepared from t-2-dimethylamino-1-hydroxyindan in the manner described for the cis-isomer 25 and was isolated in a yield of 88%, m.p. 145-149° (from ethanol and ether).

IR (nujol mull):

ν_{max} 2570 and 2400 (NH^+), 1735 (C=O) cm^{-1}.

PMR (DMSO-d_6)

δ2.18 (3H, s, acyl Me), 2.90 (6H, s, NMe_2), 6.76 (1H, d, J=6.2 Hz, H_1) this signal shifted to 6.30 after adding sodium hydroxide solution), and 7.29 (4H, m, aromatic).

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48.

Found: C, 60.79; H, 7.38; N, 5.18.

t-1-Acetoxy-2-dimethylaminoindan Methiodide (30)

t-1-Acetoxy-2-dimethylaminoindan hydrochloride (2.2 g, 8 mmol) was dissolved in ice water (10 ml) and the solution was made basic with saturated sodium bicarbonate solution then extracted with

chloroform (3 x 40 ml). Evaporation of the combined extracts (dried over Na_2SO_4) gave the free base which was then recrystallized from hexanes (b.p. 66-68°). The hydrolyzed tertiary amino-alcohol (0.55 g, m.p. 104-105°) crystallized out and was removed. The IR spectrum and m.p. of the crystals were found to be identical to that of t-2-dimethylamino-1-hydroxyindane (28). The mother liquor containing the tertiary amino-ester was concentrated. The residue was taken up in acetone and treated with excess of methyl iodide to give the title compound (1.4 g, 44%), m.p. 216-218° (from ethanol). IR (nujol mull):

ν_{max} 1740 (ester C=O), 1200 (ester C-O) cm^{-1}.

PMR (DMSO-d_6):

δ2.18 (3H, s, acyl Me), 3.24 (9H, s, $^+NMe_3$), 4.75 (1H, apparent quartet, H_2) and 6.81 (1H, d, J=5.4 Hz, H_1).

The alternate procedure, described for the preparation of the cis isomer 26, was also employed to prepare the title compound in a yield of 80%, m.p. 216-218° (from ethanol).

Attempted Synthesis of 1,1-Dimethyl-2-(N,N-dimethylamino)ethyl Benzilate (35)

The transesterification procedure of Cannon (1960) was employed. Methyl benzilate (4.64 g, 0.02 mol), 1,1-dimethyl-2-(N,N-dimethylamino)ethanol (2.34 g, 0.02 mol), sodium methoxide (0.1 g) and n-heptane (600 ml) were placed in a one liter three-neck fitted with a Dean-Stark moisture determination apparatus topped

with a condensor and a drying tube. The reaction mixture was heated under reflux, and after 1 hr sodium methoxide (0.1 g) was added. Refluxing was continued and the contents of the Dean-Stark apparatus were drained and discarded. Fresh n-heptane was added to the reaction mixture to maintain the solution volume constant. After 12 hr of reflux another 0.1 g of sodium methoxide was added and refluxing was continued for another 36 hr. The reaction mixture was cooled and washed with water until the washings were neutral to litmus paper. The solvent was removed and the residue was recrystallized from acetone and petroleum ether (b.p. 30-60°). The crystals gave a m.p. of 62-67°. One recrystallization of the crystals brought up the m.p. to 74-75°, which was found to be identical to that of methyl benzilate (Merck, 1968, 74-75°). No melting point depression was found when the product was mixed with methyl benzilate.

Synthesis of Diphenylacetyl Chloride (36)

A mixture of diphenylacetic acid (34 g, 0.15 mol) and thionyl chloride (72 g, 0.6 mol) was heated under reflux for 10 hr. Excess thionyl chloride was removed in vacuo and the residue was distilled to give the title compound (32 g, 87%), b.p. 114-116/0.2 mm, m.p. 52-54° (Merck Index, 1968, m.p. 56-57°).

1,1-Dimethyl-2-(N,N-dimethylamino)ethyl Diphenylacetate Hydrochloride (37)

The title compound was prepared from 1,1-dimethyl-2-(N,N-

dimethylamino)ethanol by the general procedure IV with the exception that diphenylacetyl chloride was employed in place of acetyl chloride, yield, 74%, m.p. 165-168° (absolute ethanol and ether).

IR (nujol mull):

ν_{max} 2650-2400 (NH), 1730 (C=O) cm^{-1}.

PMR ($CDCl_3$):

δ1.72 (6H, s, CMe_2), 2.60 (6H, br. s, NMe_2), 3.40 (2H, br. s, NCH_2), 5.10 (1H, s, Ph_2CH), and 7.33 (10H, s, aromatic).

Anal. Calcd. for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03.

Found: C, 69.10; H, 7.76; N, 3.98.

Similarly prepared was 1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-diphenylacetoxycyclohexane hydrochloride (39), yield, 78%, m.p. 183-184° (from ethanol and ether).

IR (nujol mull):

ν_{max} 2560 and 2400 (N H), 1728 (C=O) cm^{-1}.

PMR ($CDCl_3$):

δ2.60 (6H, d, J_{HNCH}=4 Hz, NMe_2), 3.67 (2H, d, J_{HNCH}=5 Hz, NCH_2), 5.83 (1H, s, Ph_2CH) and 7.33 (10H, s, aromatic).

1,1-Dimethyl-2-(N,N-dimethylamino)ethyl Diphenylacetate Methiodide (38)

The title compound was prepared from the hydrochloride 37 by the general procedure V in a yield of 91%, m.p. 145-147° (ethanol and acetone).

IR (nujol mull):

ν_{max} 1730 (C=O) cm^{-1}.

PMR ($CDCl_3$):

δ1.77 (6H, s, CMe_2), 3.22 (9H, s, NMe_3), 4.07 (2H, s, NCH_2), 5.10 (1H, s, Ph_2CH), and 7.35 (10H, s, aromatic).

Anal. Calcd. for $C_{21}H_{28}INO_2$: C, 55.64; H, 6.22; N, 3.09.

Found: C, 55.01; H, 6.21; N, 2.77.

Similarly prepared was 1-(N,N-dimethylaminomethyl)-c-3-methyl-r-1-diphenylacetoxycyclohexane methiodide (40) (98%), m.p. 179-181° (absolute ethanol and acetone).

IR (nujol mull):

ν_{max} 1730 (C=O) cm^{-1}.

PMR ($CDCl_3$):

δ3.30 (9H, s, NMe_3), 4.30 (2H, s, NCH_2), 5.03 (1H, s, PhCH), and 7.35 (10H, s, aromatic).

Anal. Calcd. for $C_{25}H_{34}INO_2$: C, 59.17; H, 6.75; N, 2.76.

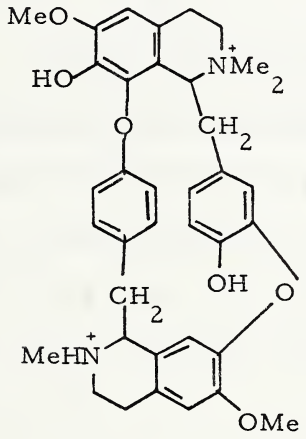
Found: C, 59.32; H, 6.82; N, 2.76.

PART II

SYNTHESIS AND PHARMACOLOGY OF SOME NEUROMUSCULAR BLOCKING AGENTS

INTRODUCTION

Neuromuscular blocking agents are a class of compounds which mainly interrupt transmission of nerve impulses at the skeletal neuromuscular junctions. On the basis of the mechanism by which they produce this effect they may be classified into three categories (Goodman and Gilman, 1971): i) competitive agents are those which compete with acetylcholine (ACh) for its receptor, thereby preventing acetylcholine from exerting its depolarizing effect. (e.g. (+)-tubocurarine (51) and gallamine (52)), ii) depolarizing agents which



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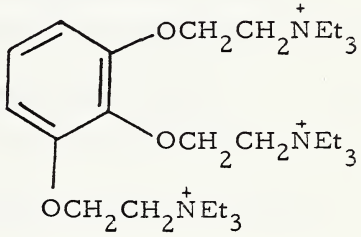
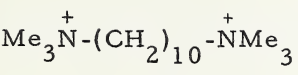


51 52

resemble ACh in its action on the motor end-plate region, causing electrical inexcitability which is much more prolonged than that produced by the natural transmitter, ACh. (e.g. decamethonium (53) and suxamethonium (54)), and iii) the agents with the



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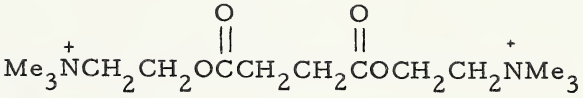

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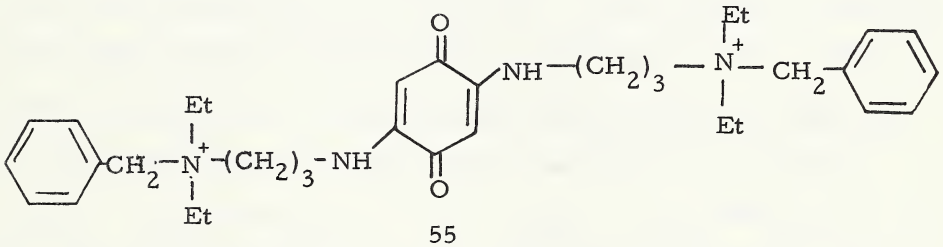
combined actions of i) and ii) such as benzoquinonium (55).



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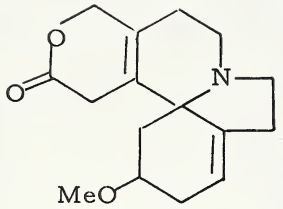
Compounds of diverse structures exhibit neuromuscular blocking activity but in general they require a strong basic centre capable of existence as a positively charged ion. According to their chemical structures these agents may be divided into the following groups: i) active tertiary bases, ii) monoquaternary ammonium compounds, iii) bis-onium compounds and iv) tris-onium compounds.

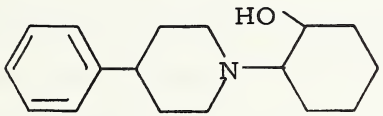
i) Active Tertiary Bases

The Erythrina alkaloids are naturally occurring tertiary bases which exhibit curare-like activity. The most active member of the alkaloids, dihydro-β-erythrodine (56), possesses about one-third of the potency of (+)-tubocurarine on the rat diaphragm preparation (Unna et al., 1944). The curarizing potency is markedly



56

reduced on conversion to the methiodide. This behavior is contrary to most other tertiary amines (Salama and Wright, 1951). Other tertiary amines (e.g. 2-(4-phenylpiperidino)cyclohexanol (57) and its methiodide (58)) also demonstrate neuromuscular blocking



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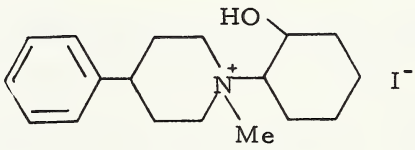
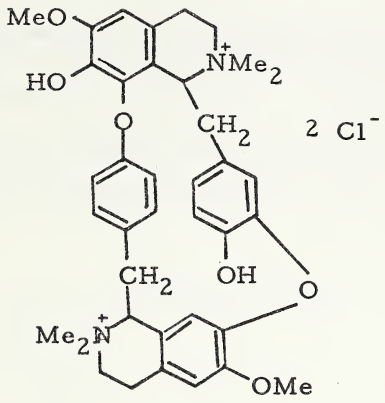


58

activity (Marshall, 1970), and it has been found that quaternization reduces neuromuscular blocking activity by eight to ten fold.

ii) Bis-onium Compounds

Most neuromuscular blocking agents fall in the bis-onium compounds category. Curare alkaloids have been well known for several decades as potent agents and are widely used clinically. Interestingly, the long accepted structure for (+)-tubocurarine chloride (59) has recently been found to be incorrect. The correct structure, instead of having two quaternary groups, has only one quaternary centre, together with a protonated tertiary nitrogen (Everett et al., 1970). However, the long accepted bis-onium



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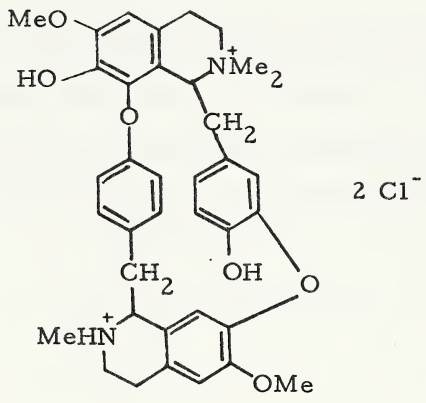


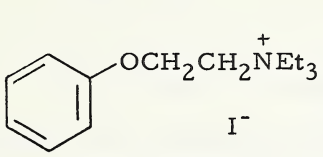
51 (correct structure)

feature of (+)-tubocurarine led to the subsequent discovery of many bis-onium compounds possessing neuromuscular blocking activity, and among these compounds suxamethonium (53) (Bovet et al., 1949) and decamethonium (54) (Paton and Zaimis, 1949; Barlow and Ing, 1948). are, or have been widely used. The SAR studies of 53 and 54 gave rise to the suggestion that the two quaternary moieties of either molecule attached to two receptors or to one receptor and one "anchoring" site at a definite distance apart on the biological surface. The optimal separation between the onium groups was found to be 10 - 14 Å (Barlow and Ing, 1948; Paton and Zaimis, 1948). This is known as the two point-attachment hypothesis.

iii) Tris-onium Compounds

Gallamine (52) was reported as a potent neuromuscular blocker by Bovet and others (1946) and has enjoyed extensive clinical

application. It was found that the tris-onium feature contributed to the potency of this type of compound (Bulbring and Depierre, 1949). Reduced activity was observed in the corresponding monoquaternary compound 60 and bisquaternary compound 61 ; the former had 1/4



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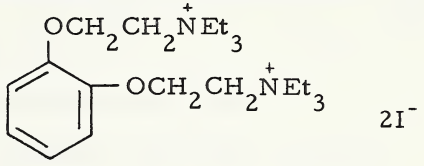

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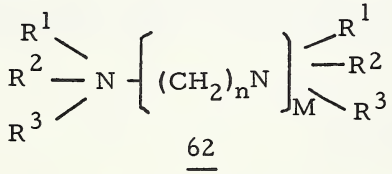
and the latter had 1/50 of the potency of gallamine when tested on the rat diaphragm. A series of linear polyonium compounds

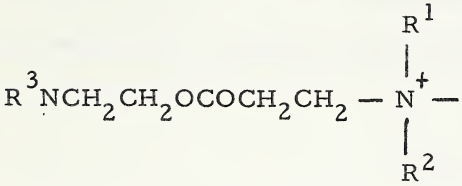


62

R = alkyl
M = 1 ∽ 5
n = 6 ∽ 10

was reported to have neuromuscular blocking activity (Edwards et al., 1957; 1958a; 1958b). In general, an increase in blocking potency was observed with the increase in the number of onium groups, and the observation provided an argument for a repeating arrangement of suitably spaced anionic receptors on the motor end-plate. The potency of these compounds was comparable to that of (+)-tubocurarine. Tris-onium compounds (63) in which part of methylene linkage was replaced by an ester function were also reported to have

neuromuscular blocking activity (Marshall, 1968), but no comparison



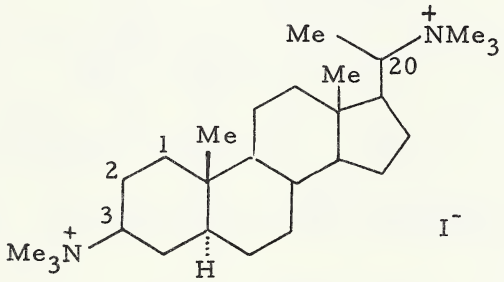
63

R^1, R^2 and R^3 = alkyl or part of alicyclic ring

of potency was made between these compounds and other standard neuromuscular blockers such as suxamethonium.

iv) Monoquaternary Ammonium Compounds and Neuromuscular Blocking Agents with a Steroidal Nucleus

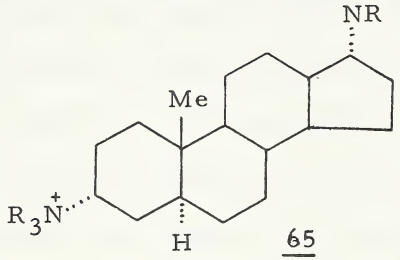
In 1960 the neuromuscular blocking activity of a natural alkaloid, malouetine (64), was noted (Quevauviller and Laine, 1960);



64 (3β, 20α)

it had approximately 75 percent of the potency of (+)-tubocurarine in the rabbit head-drop test. The other three isomers of 64, 3β,20β-, 3α,20α- and 3α,20β- were tested (Khuong Huu-Laine & Pinto-Scognamiglio, 1964) and the potencies were found to be approximately the same for all four isomers. Similar work was carried out by others. Alauddin (1965), reported that the incorpor-

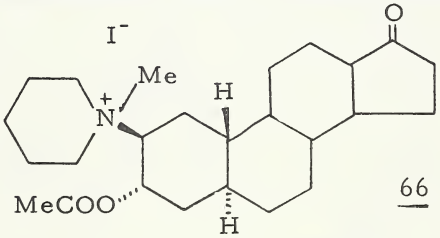
ation of the androstane skeleton into bis-onium compounds resulted in potent neuromuscular blocking agents. Only small differences in potency were noted among the four analogs of 65. Lewis et al. (1967)



R = Me or Et

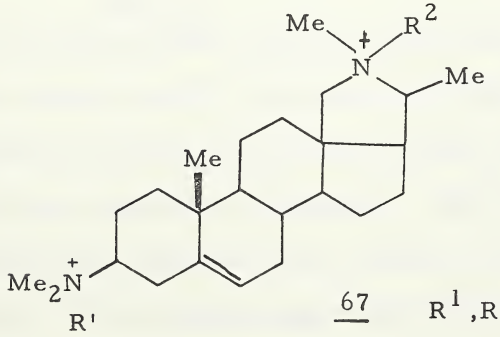
65

reported that monoquaternary ammonium salts with androstane or pregnane skeletons possessed neuromuscular blocking activity. The most active member, 3α-acetoxy-2β-piperidino-5α-androstan-17-one (66) was 1/16 as active as (+)-tubocurarine in cats. Connesine



66

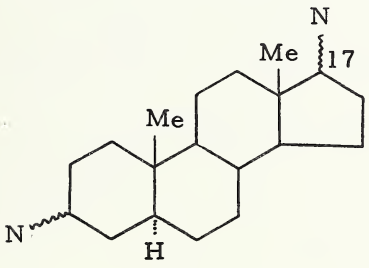
alkaloids 67 (Busfield et al., 1968) were also shown to be as potent



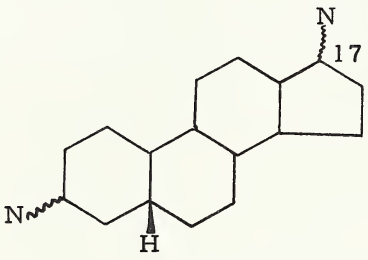
67 R^1, R^2 = Me, Et, Bu, Ph etc.

as (+)-tubocurarine. It was observed that changing the quaternizing

group in mono- and bis-quaternary compounds exerted little effect on potency and duration of the neuromuscular blockade. The similarity in activity of these compounds seemed to support the one-point attachment theory of Loewe and Harvey (1952). This theory differed from that proposed by Barlow (1949) and Paton (1948) in that only one site on the receptor was held to be responsible for the binding of bis-onium. The rest of the bis-onium molecule afforded an "adumbrating" influence which might hamper the access of the transmitter or other material to the receptor site. Further studies on mono- and di-quaternary ammonium compounds based on the androstane skeleton were carried out (Bamford et al., 1971; 1967). It was found that in both the 5α (68) and 5β (69) series, the steroids with 3β configuration in all



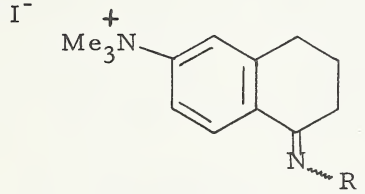
68 (5α)



69 (5β)

cases showed higher activity, while the configuration at C_5 and C_{17} was unimportant for neuromuscular blockade. Replacement of the quaternary group at C_{17} with a tertiary amine resulted in a compound with equal potency to the parent. However, a sharp decrease in activity was observed when a ketone or hydroxyl group was placed at C_{17}. The results suggest that potent neuromuscular blockers must possess a fully quaternized ammonium group and another

electronegative feature which is capable of protonation to provide an additional cationic head for "anchoring" the molecule to the receptor. It is interesting to note that the corrected structure of (+)-tubocurarine supports this view. A new type of neuromuscular blocking agent based on tetralone (70) has been made by Bamford et al. (1969).



$R = NH_2$, $\overset{O}{\overset{\|}{C}}-NH_2$ etc

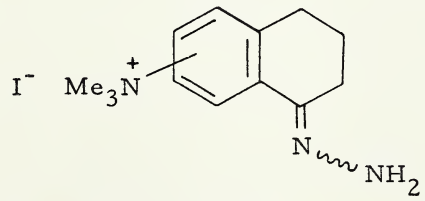
70

These compounds were found to be as potent as suxamethonium, and also had the characteristic of being mono-quaternary salts.

AIMS AND OBJECTIVES

Nicotinic agonists are known to be non-stereospecific. However, nicotinic antagonists such as d-tubocurarine do demonstrate this specificity (Stenlake, 1963). Decamethonium and succinylcholine are flexible molecules. The SAR studies derived from these molecules may be deceptive. Tetralone compounds have been demonstrated to possess potent neuromuscular blocking activity (Bamford et al., 1969). It was decided to extend their work because: i) these compounds were potent depolarizing neuromuscular blocking agents ii) they provided a relatively rigid structure and the distance between the nitrogen atoms can be easily determined. The present SAR studies of the tetralone compounds involves the following aspects.

i. Effect of changing the relative distance between the quaternary ammonium group and the carbonyl substituent (generally a hydrazone). To this end, positional isomers of the tetralone compounds were made and tested.



78 6-$\overset{+}{N}Me_3$

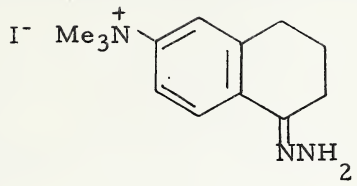
88 7-$\overset{+}{N}Me_3$

98 5-$\overset{+}{N}Me_3$

103 8-$\overset{+}{N}Me_3$

ii. Investigation of the configuration of the hydrazone moiety, and the effect of N,N-dimethylation of the hydrazone (106, 107).

iii. Effect of reduction of the aromatic ring of the tetralone compound (78) to (121).



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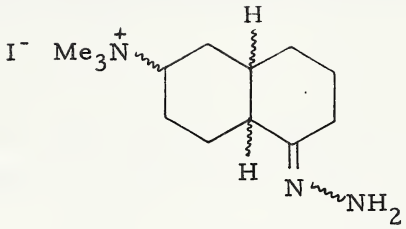
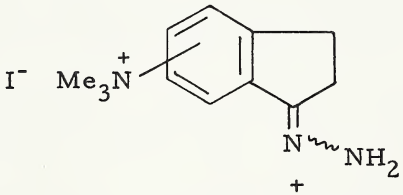


121

iv. A study of the corresponding indanones (144, 135, 141).



144 4-$\overset{+}{N}Me_3$-

135 5-$\overset{+}{N}Me_3$-

141 6-$\overset{+}{N}Me_3$-

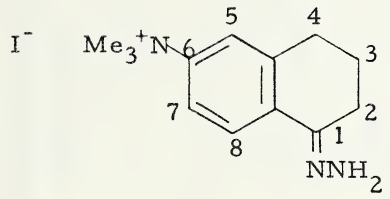
CHEMISTRY DISCUSSION

SYNTHESIS OF AMINOTETRALONE HYDRAZONE METHIODIDES AND TOSYLATE

In 1969 Bamford and others made some neuromuscular blocking agents based on 1-tetralone. Pharmacological data on the most active member 78 and some of its analogs are given in Table 6

It can be noted from the table that the ED_{50} for compound (Table 6 , $R^2 = CH_3$, $R^1 = NH_2$, salt) is 8.7×10^{-8} mol/kg. The potency is approximately the same as that of suxamethonium bromide (7.1×10^{-8} mol/kg). It was decided to extend Structure-Activity Relationship studies on the most active compound 78 .

The synthesis of the following compounds was attempted; of these only compound 103 could not be made and a possible explanation for this failure will be given later.



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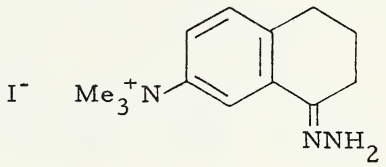

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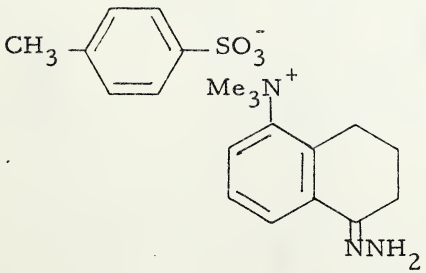

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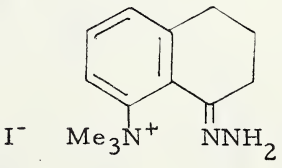

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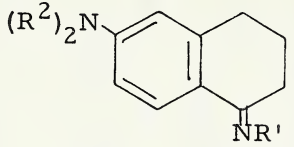
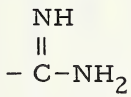
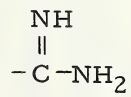
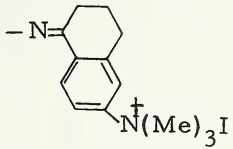
Table 6 Neuromuscular Blocking Activity of Some Amino-1-tetralones.



R^2	R^1	Salt	Pharmacological Results			
			LD_{50} (mol/kg)	ED_{50} (mol/kg)	[a] D_{50} mins	[b] Test method
H		2HCl	8.5×10^{-5}	3.3×10^{-5}	2.5	D
Me		MeI and HI	2.1×10^{-5}	2.0×10^{-5}	-	
Me	$-NH_2$	MeI	0.2×10^{-5}	8.7×10^{-8}	4	D
Me		MeI	0.1×10^{-5}	3.7×10^{-8}	12.0	C
Suxamethonium bromide	-	-	-	7.1×10^{-8}	-	D
Gallamine triethiodide	-	-	-	6.6×10^{-7}	-	C

a. D_{50} Duration of action in mins.
b. Tested on the sciatic nerve and tibial muscle preparation of the cat, where D = Depolarizing, C = competitive

6-Dimethylamino-1-tetralone Hydrazone Methiodide (78)

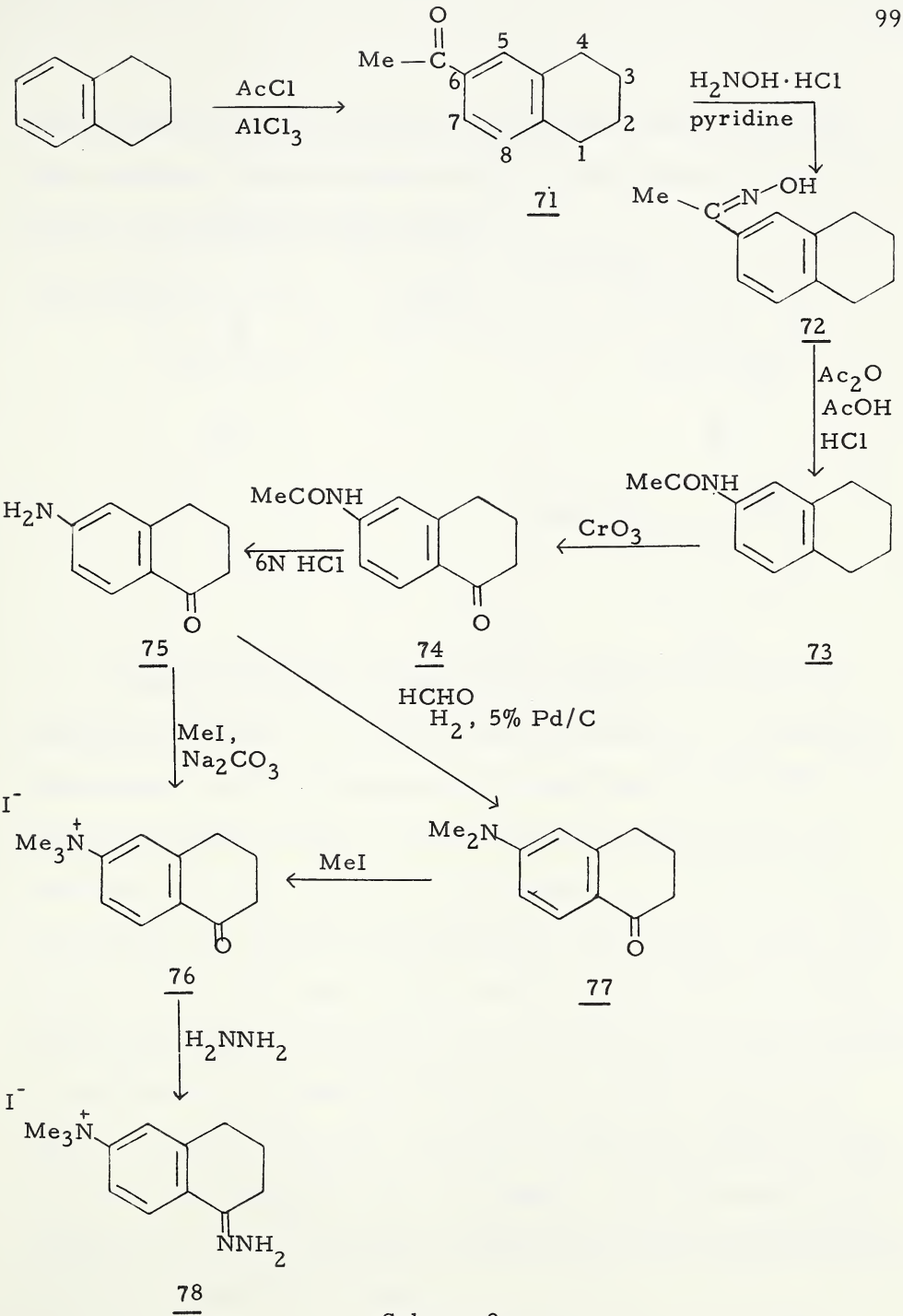
Compound 78 was prepared following the procedure of Bamford et al. (1969) with some modifications. Compound 78 was made as a reference standard in the pharmacological studies. The scheme of the synthesis is shown below.

The Friedel-Crafts acylation of tetralin, in theory, could lead to a mixture of 5-acetyltetralin and 6-acetyltetralin (71). The acylation of tetralin following the procedure of Schofield et al. (1949) gave exclusively 6-acetyltetralin (71). The PMR spectrum of compound 71 displayed one doublet (J = 8.5 Hz) at δ 7.05, and this signal could be assigned to H_8 which coupled to H_7. No meta coupling was found for H_8; this suggested that C_6 was substituted with acyl group.

The amide 73 was obtained through a Beckmann rearrangement. The reagents which promote the rearrangement are usually i) benzene sulfonyl chloride in pyridine, ii) hydrogen chloride in acetic acid, or iii) phosphorus pentachloride in ether (Fieser and Fieser, 1961).

Allinger and Jones (1962) employed the first reagent. However, in the present study the second reagent was more suitable; the product was easily purified and formed in a better yield.

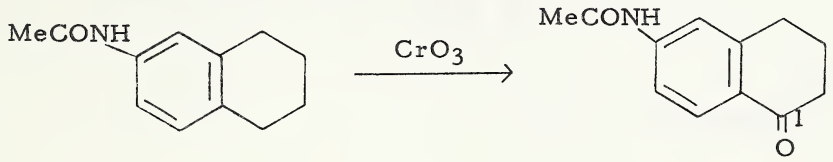
The conversion of 6-acetyltetralin (71) into its oxime derivative 72 was indicated by a loss of carbonyl stretching in the IR spectrum of 72. The amide 73, obtained from the oxime 72, showed a strong amide I band at 1683 cm^{-1}, which was absent in 72.



71 72 73 74 75 76 77 78

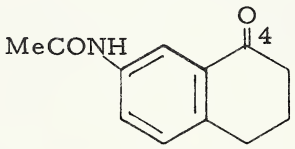
Scheme 9

The oxidation of 73 with chromium trioxide (in acetic acid) under mild condition could yield theoretically two isomers as a result of oxidation of a benzylic carbon atom.



73 74

+



86

The preferential formation of the 1-tetralone 74 may be explained as follows: It is known that the oxidation of a methylene into a ketone function is initiated by an attack at a benzylic CH (Wiberg and Evans, 1960). The intermediate formed by the C-H attack may be a free radical or a carbonium ion, and both species are stabilized by electron-donating groups (Wiberg and Evans, 1960; Rocek, 1962). The nature of the oxidative intermediate of 6-acetylamidotetralin (73) is not known, but it is certain that the intermediate is stabilized by 6-acetamido group through a positive mesomeric effect. In the present case, the positive mesomeric effect can only operate at C_1-H (para) but not C_4-H (meta). As a consequence, the oxidation at C_1-H is facilitated as compared to C_4-H, and thus 74 is the preferred oxidation product.

The PMR spectrum of 74 shows a well resolved aromatic

signal (see Figure 2).

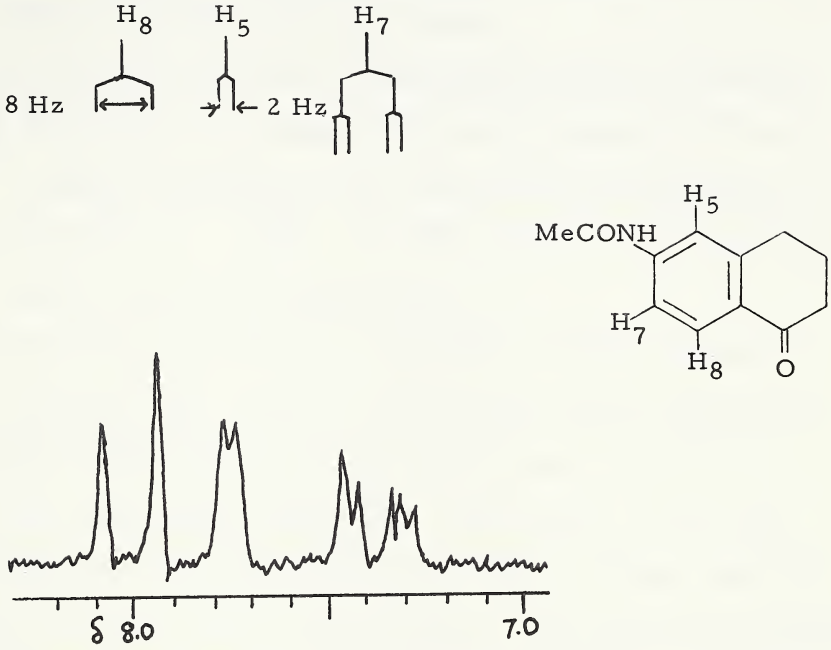


Figure 2 Part of PMR spectrum of 6-acetamido-1-tetralone (74) at 60 MHz in $CDCl_3$.

The aromatic region of compound 73 was irresolvable because the chemical shift difference, $\Delta\delta$, of the three aromatic protons approached their J values. However, the magnitude of $\Delta\delta$ was large as compared to J in compound 74 and permitted a first order analysis (Jackman and Sternhell, 1969). This was due to the deshielding effect of the ketone oxygen atom at C_1, which strongly deshielded the proton (H_8) at the ortho position. H_8 and H_7 coupled to give a pair of doublets with a J value (8 Hz) typical of ortho coupling (Bovey, 1969). The doublet which arose from H_7 was further split by H_5 (meta coupling) into a doublet of doublets (J = 2 Hz). Moreover, the

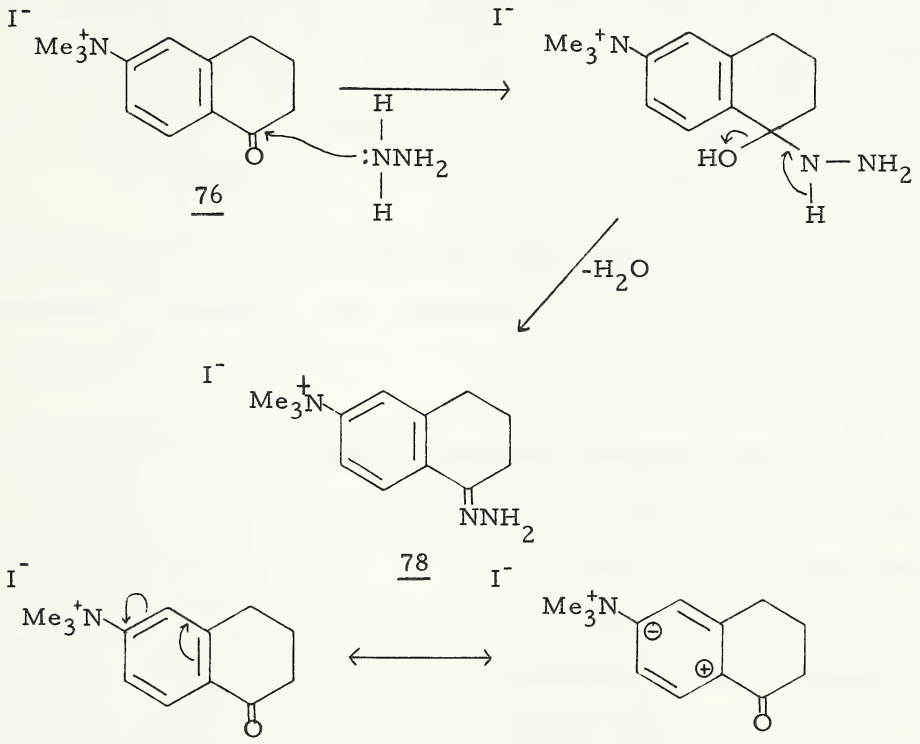
downfield shift of H_8 (relative to H_5 and H_7) in compound 74 was a good indication of oxidation at the C_1- carbon.

Acid catalyzed hydrolysis of 74 yielded 6-amino-1-tetralone (75). The IR spectrum of compound 75 gave two bands at 3405 and 3330 cm^{-1}, typical of asymmetric and symmetric N-H stretching of a primary amine (Bellamy, 1958). Its PMR spectrum showed similar aromatic signals to those of compound 74 .

Conversion of the primary amine 75 to 6-dimethylamino-1-tetralone methiodide (76) resulted in the aromatic protons H_5 and H_7 being deshielded by the quaternary ammonium group, whence their chemical shifts approached that of H_8. As a result, $\Delta\delta$ was too small between each of the three protons and their couplings could not be analyzed by the first order approximation. A group of irresolvable peaks centered at δ 8.05 represented the three protons.

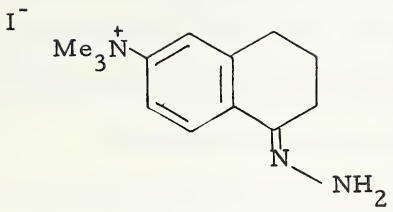
The formation of 6-dimethylamino-1-tetralone hydrazone methiodide (78) was effected by refluxing the corresponding ketone (76) with hydrazine for 2-3 hr. However, the same procedure, when employed to make the C_5 and C_7-dimethylamino substituted isomers, invariably gave back the starting materials. It was found that an overnight reflux period was required to make C_5 and C_7 substituted hydrazones, i.e., compounds 98 and 88. This observation seemed to indicate that the formation of 78 was promoted by positioning the trimethylamino group at C_6 but not at C_5 or C_7. A rationalization follows. The reaction of a hydrazine and a ketone is believed to be initiated by a nucleophilic attack of hydrazine on the carbonyl carbon;

then the hydroxyl group is removed and the carbon-nitrogen double bond forms (see Scheme 10) (March, 1968).

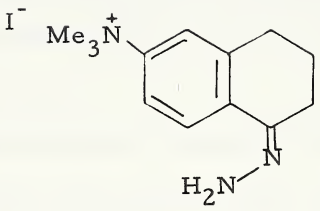


It can be seen that the C_1-carbon in the more favored form is flanked by the two electron withdrawing features and thus activated toward a nucleophilic attack; this arrangement cannot arise when $^{+}NMe_3$ is at C_5 or C_7.

Theoretically, it is possible for compound 78 to exist in two geometrically isomeric forms, NH_2 being syn or anti to the aromatic ring.



anti

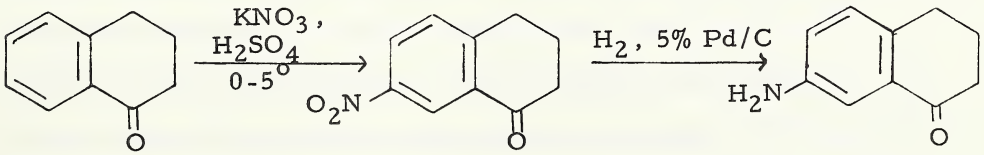


syn

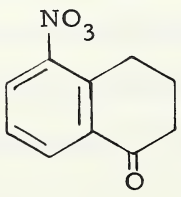
However , it is probable that the anti isomer is the only one obtained. Support for this assignment will be given in the next section.

7-Dimethylamino-1-tetralone Hydrazone Methiodide (88)

Various ways were sought to make 7-amino-1-tetralone (81), the key intermediate required for the synthesis of 88 . The literature method (Schroeter , 1930) used 1-tetralone as a starting material; this was nitrated to give 7-nitro-1-tetralone (79), which was then catalytically hydrogenated at atmospheric pressure to yield 81 (Scheme 11). Another method to synthesize compound 81 , devised



79 (major isomer) 81



80 (minor isomer)

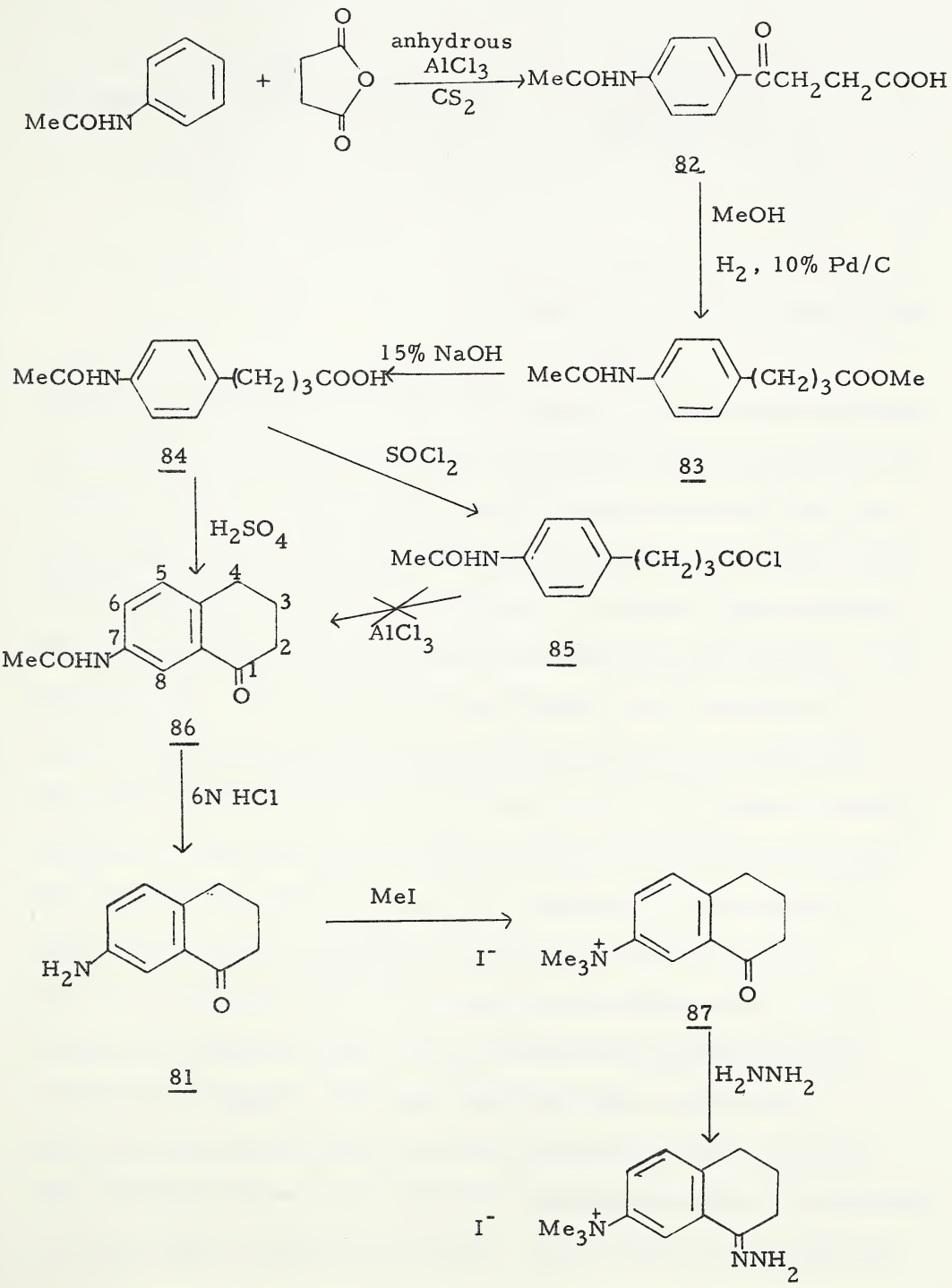
Scheme 11

in the present study, involve making the appropriately substituted phenylbutyric acid which was cyclized (see Scheme 12) to the acetylated aminotetralone (86).

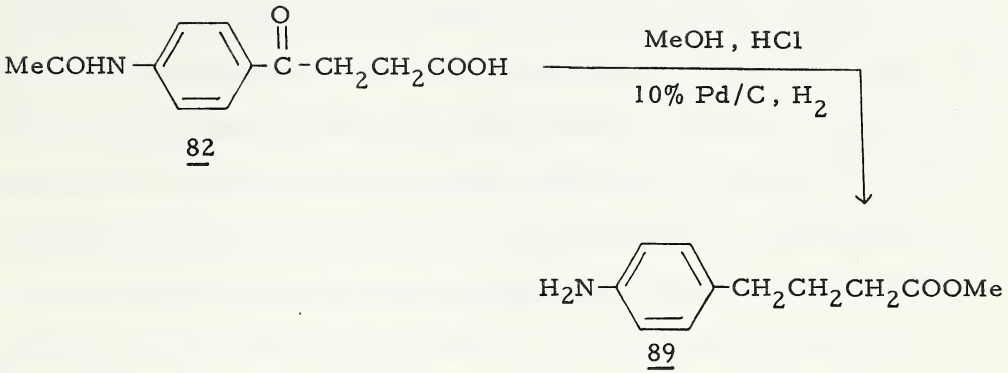
This procedure has more steps than the literature method but was chosen due to a lack of 1-tetralone at the time of this investigation.

3-(p-Acetamidobenzoyl)propionic acid (82) was prepared by the literature procedure (Clapp et al., 1948) in a yield of 30%. The IR spectrum of this compound showed three carbonyl absorption bands at 1710, 1682 and 1655 cm^{-1}, typical of carbonyl bands for carboxylic acid, aromatic ketone and amide I band respectively. The PMR spectrum indicated a characteristic para substituted pattern as a pair of symmetrical doublets (4 protons) appeared near δ 7.85.

It is reported (Martin, 1943) that the ketone group of 3-benzoylpropionic acid can be reduced to methylene by zinc amalgam and hydrochloric acid. The Huang-Minlon reaction is an alternative means of accomplishing this type of reduction. Both procedures were thought to be too vigorous for the present case because the acetamido-group of compound 82 could be hydrolyzed during the process. Instead, it was considered that, under catalytic hydrogenation, the carbonyl group would first be reduced to an alcohol of the benzylic type, which would subsequently be hydrogenolyzed to a methylene group. Phillips and Mentha (1963) hydrogenated compound 82 in the presence of hydrochloric acid and metnanol. They were able to obtain the corresponding aminoester of compound 89 (see the reaction below).


MeCOHN
anhydrous AlCl3 / CS2
MeCOHN CCH2CH2COOH
82
MeOH
H2, 10% Pd/C
MeCOHN (CH2)3COOMe
83
15% NaOH
MeCOHN (CH2)3COOH
84
SOCl2
MeCOHN (CH2)3COCl
85
AlCl3
H2SO4
86
6N HCl
H2N
81
MeI
I-
Me3N+
87
H2NNH2
I-
Me3N+
NNH2
88

Scheme 12



82 89

Without using hydrochloric acid in the catalytic reduction the acetamido-ester should be obtained since hydrolysis of the amide group would not be likely. Thus, catalytic hydrogenation and subsequently hydrogenolysis were carried out using 10% Pd/C in methanol as solvent. The product after being worked up was found to be methyl 4-(p-acetamidophenyl)butyrate (83). Esterification accompanied the catalytic hydrogenation. The ester without purification was hydrolyzed by means of 15% sodium hydroxide in water to the corresponding acid. The period of hydrolysis was found to be crucial. A 15 minute heating period on a steam bath was adequate; more prolonged heating caused hydrolysis of the amide function also. Successful cyclizations of phenylbutyric acids to 1-tetralones have been reported by using anhydrous aluminum chloride, phosphorus oxychloride and conc. sulfuric acid (Sethna, 1964). Use of anhydrous aluminum chloride was first investigated. The acid chloride of 85 was made and cyclized by an intramolecular Friedel-Crafts procedure. Reaction time and temperature were varied, but the desired product, 7-acetamido-1-tetralone (86) could not be obtained. This failure can be explained

as follows. Friedel-Crafts reactions may be considered as an electrophilic substitution of a carbonyl group on an aromatic ring. The reactivity and orientation of substitution are affected by the substituent which is already present on the ring. In this case, the acetamido group activates para and ortho positions. The position where cyclization should occur is meta to the acetamido substituent and hence is not specially activated. A similar failure has been noted in attempts to cyclize 4-(6-methoxyphenyl)butyric acid which also carries an o or p directing substituent meta to the cyclization position (Campbell, 1942). In addition, an intermolecular Friedel-Crafts reaction may occur at the position ortho to the acetamido group and lead to a polymerized product. Failure to recover the starting material or the corresponding acid indicates that this reaction possibly happens.

Lockett and Short (1939) reported that 4-(p-methoxyphenyl)-butyric acid could be cyclized with phosphorus oxychloride, a reagent which could overcome difficulties caused by electron-donating nature of the methoxyl group. Unfortunately, it failed to cyclize 4-(p-acetamidophenyl)butyric acid (84).

Initially sulfuric acid was not considered as a cyclizing agent because it might cause hydrolysis of the acetamido group and sulfonation of the aromatic ring. Finally, however, use of sulfuric acid was investigated. By varying reaction temperature and time it was found that hydrolysis could be avoided, and at the same time the cyclization effected. On further consideration, sulfonation

appears unlikely as a competition to cyclization because all available positions are adjacent to substituents and hence unfavored in this sterically retarded reaction (Fieser and Fieser, 1961). The optimal condition of cyclization with sulfuric acid was found to be 80^{o} for 16 hr. Higher reaction temperatures produced hydrolysis, and lower ones did not induce cyclization. A reaction time of 16 hr gave the best yield; longer or shorter times reduced the yield.

The IR spectrum of the product showed two bands at 1670 and 1695 cm^{-1} characteristic of amide and ketone carbonyl stretching bands respectively. The immediate precursor, compound 84, gave an acid carbonyl stretching band at 1715 cm^{-1}. The PMR spectrum of the tetralone 86 was well resolved. The aromatic protons showed a typical first order splitting pattern. Among the aromatic signals, that of H_5 appeared at the highest field, probably due to the electron donating effect of the methylene group, H_6 (weakly deshielded by NHCOMe) had an intermediate, and H_8 (strongly deshielded by the adjacent C=O group) had the lowest field. The 3 J values are consistent with these assignments. (See Figure 3).

The amide 86 was hydrolyzed with 6N HCl in the same manner as 74 in quantitative yield. The IR spectrum of the amino compound 81 displayed two bands at 3340 and 3440 cm^{-1} typical of asymmetric and symmetric NH stretching. The compound was not stable in solution and its PMR spectrum could not be recorded (it resinified in $CDCl_3$).

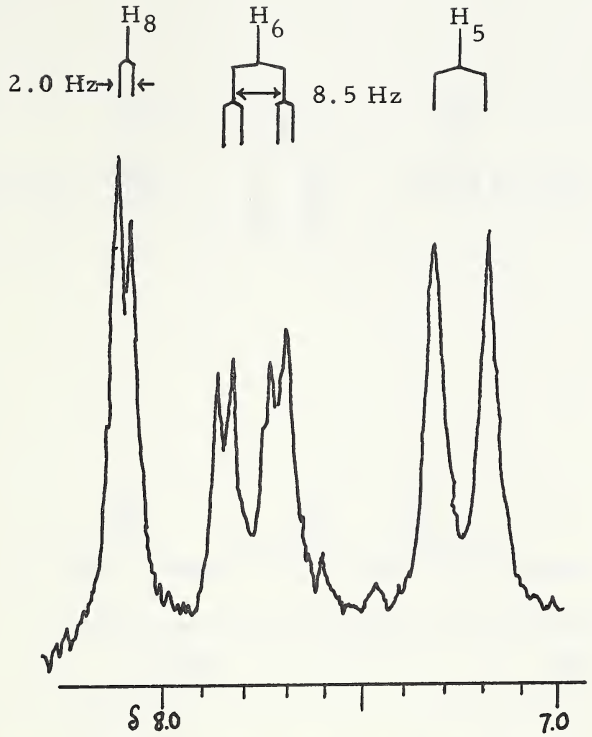


Figure 3 Part of PMR spectrum of 7-acetamido-1-tetralone (86) at 60 MHz in DMSO-d_6.

7-Dimethylamino-1-tetralone methiodide (87) was prepared in the same manner as described for its 6-amino analog 76. The IR spectrum showed no NH stretching band, an indication of complete methylation. The PMR spectrum exhibited a singlet at δ 3.70 (9 protons), characteristic of the $^{+}NMe_3$ signal and a complex aromatic signal. The hydrazone 88 was synthesized as described for the 6-amino analog 78. The aromatic PMR signals were very well resolved and the assignments were the same as that of 88. (Figure 4).

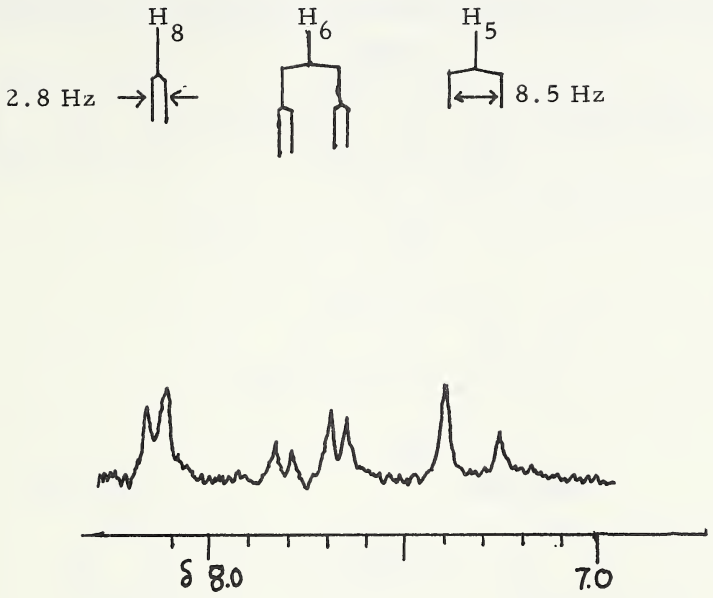
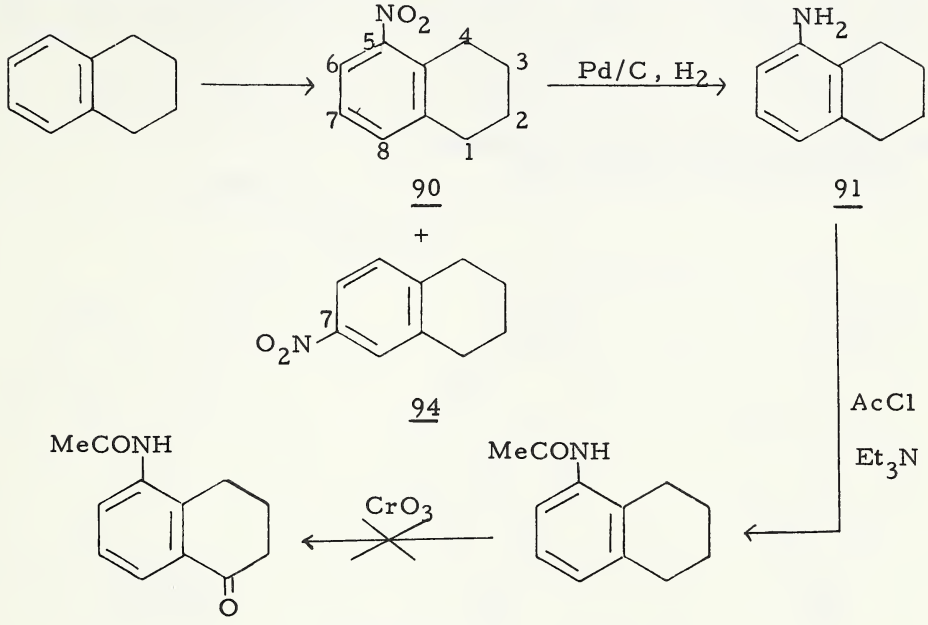


Figure 4 Aromatic signals of PMR spectrum of compound 88 at 60 MHz in DMSO-d_6.

5-Dimethylamino-1-tetralone Hydrazone Methyl Tosylate (98) and Attempted Synthesis of 8-Dimethylamino-1-tetralone Hydrazone Methiodide (103).

The syntheses of these two compounds are discussed together because both preparations involve the same pathway. Synthetic routes to the two intermediates, 5-nitro-1-tetralone (80) and 8-nitro-1-tetralone (95) were sought. Schroeter (1930) reported that nitration of 1-tetralone yielded 5- and 7-nitro-compounds. This method was not satisfactory for the present study because the 5-nitro compound 80 only formed as a minor isomer. An attempt was made to prepare 5-amino-1-tetralone (99) by a route similar to that described for the

synthesis of 6-amino-1-tetralone (75) (see Scheme 13).

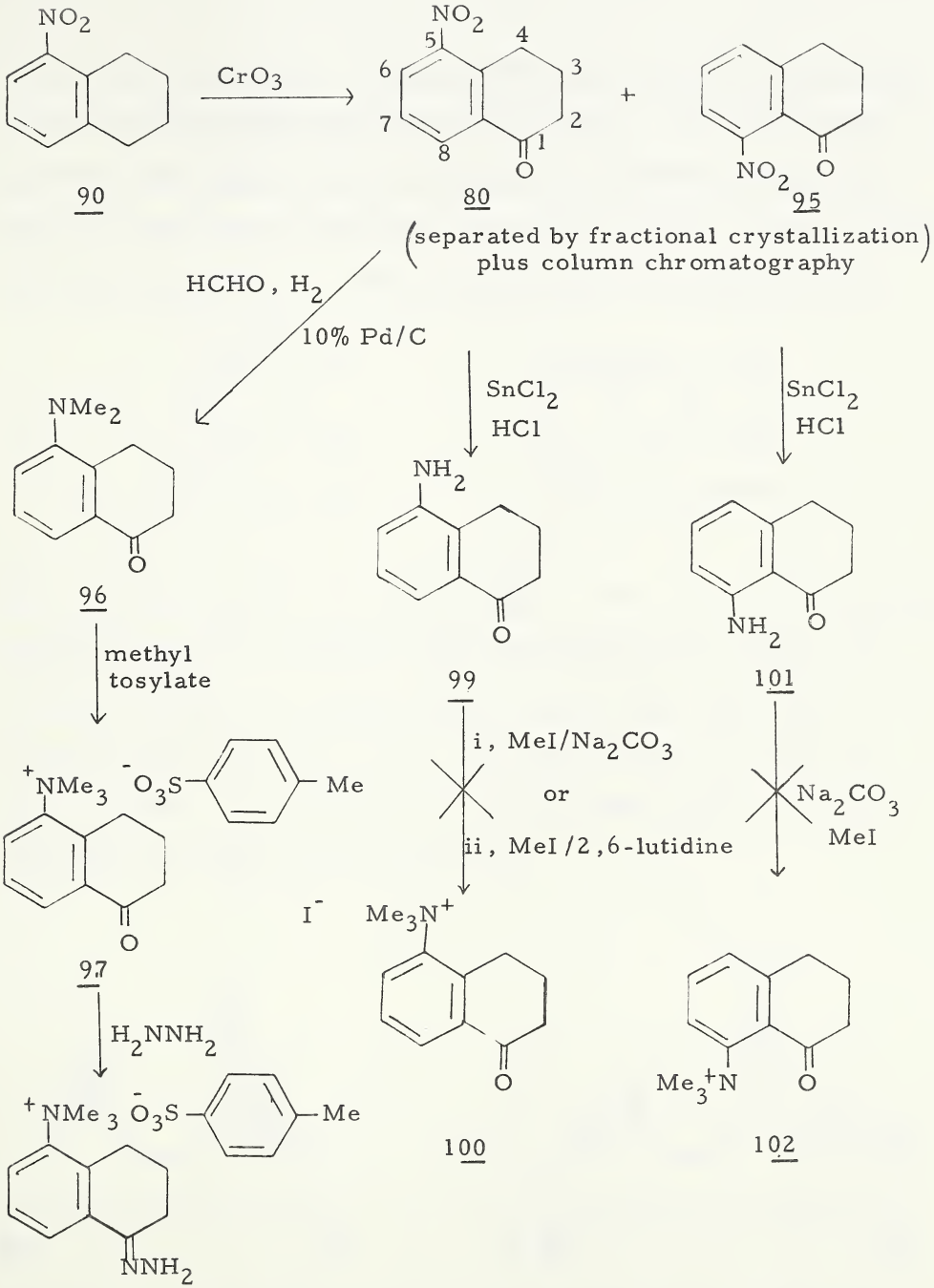


Scheme 13

5-Acetamidotetralin (92) was synthesized without difficulty by the sequence 90 through 92. However, the oxidation of compound 92 imposed many problems. Various reaction conditions and solvents were used but the oxidation product 5-acetamido-1-tetralone (93) could not be formed.

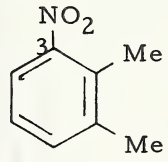
Finally the following synthetic route (Scheme 14) was chosen. This route is not ideal and its disadvantages will be discussed subsequently. Since there were no other practical routes, this procedure was used.

5-Nitrotetralin (90) was prepared by a reported procedure (Schroeter, 1922). In order to obtain a product free from 6-nitrotetralin (see Scheme 14), repeated fractional distillations of the

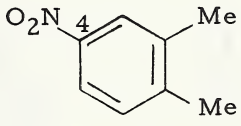

NO2
CrO3
NO2
5
4
6
3
7
2
8
1
O
+
NO2
O
90
80
95
(separated by fractional crystallization plus column chromatography)
HCHO, H2
10% Pd/C
SnCl2
HCl
SnCl2
HCl
NMe2
O
NH2
O
NH2
O
96
99
101
methyl tosylate
i, MeI/Na2CO3
or
ii, MeI/2,6-lutidine
Na2CO3
MeI
+NMe3 -O3S
Me
O
I-
Me3N+
O
Me3+N
O
97
H2NNH2
+NMe3 -O3S
Me
NNH2
98
100
102

Scheme 14

mixture were necessary. This operation was a serious disadvantage because it lowered the yield and consumed time. To confirm that 5-nitrotetralin (90), was the correct isomer, its PMR spectrum was compared with those of reference compounds, namely, 3-nitro-o-xylene and 4-nitro-o-xylene. 3-Nitro-o-xylene may be regarded as the



3-nitro-o-xylene



4-nitro-o-xylene

ring-opened analog of 5-nitrotetralin (90). Thus, the aromatic proton signals of these two compounds were anticipated to be similar. It was observed that the aromatic proton signal of 90, although not resolved in the first order sense, was nearly identical to that of 3-nitro-o-xylene. The aromatic parts of the PMR spectra of the two compounds are shown below (Figure 5).

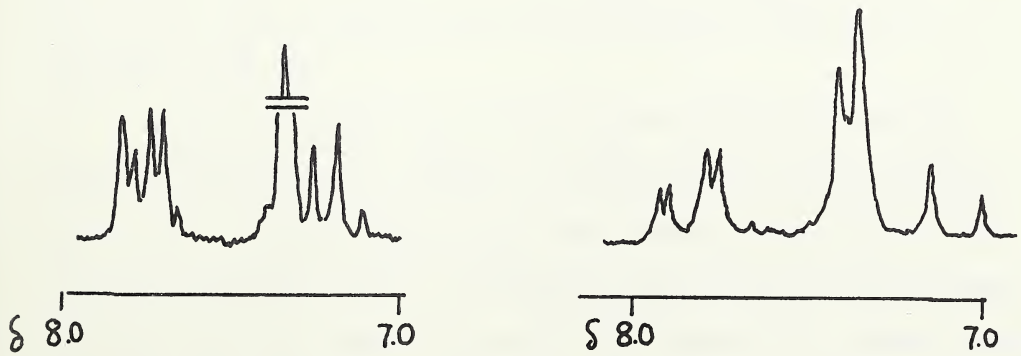


Figure 5 Part of PMR spectra of 5-nitrotetralin (left) and 3-nitro-o-xylene (right) both recorded at 60 M Hz in CCl_4.

The PMR spectra of analogs 6-nitrotetralin (94) and 4-nitro-o-xylene were obtained to serve the purpose of comparison, as shown in Figure 6 . It can be seen that the aromatic signals of these two

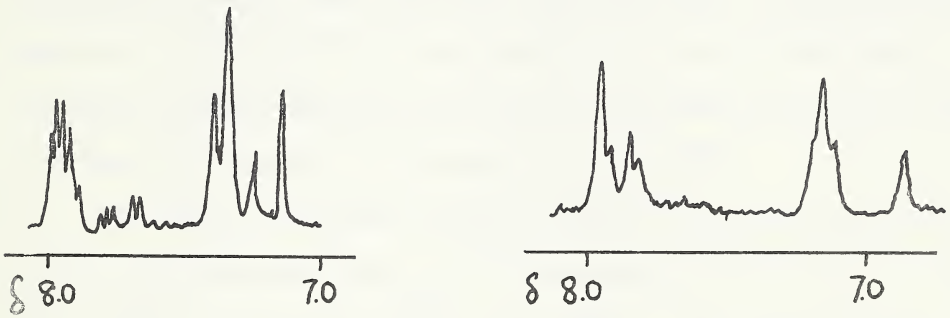


Figure 6 Part of PMR spectra of 6-nitrotetralin (94) (left) and 4-nitro-o-xylene (right) at 60 MHz in CCl_4.

compounds are almost identical as anticipated from their identical substitution pattern. A mixture of 50% of each of 3-nitro- and 4-nitro-o-xylene was found to have a PMR spectrum very similar to that of the original product (prior to fractionation) obtained by nitration of tetralin.

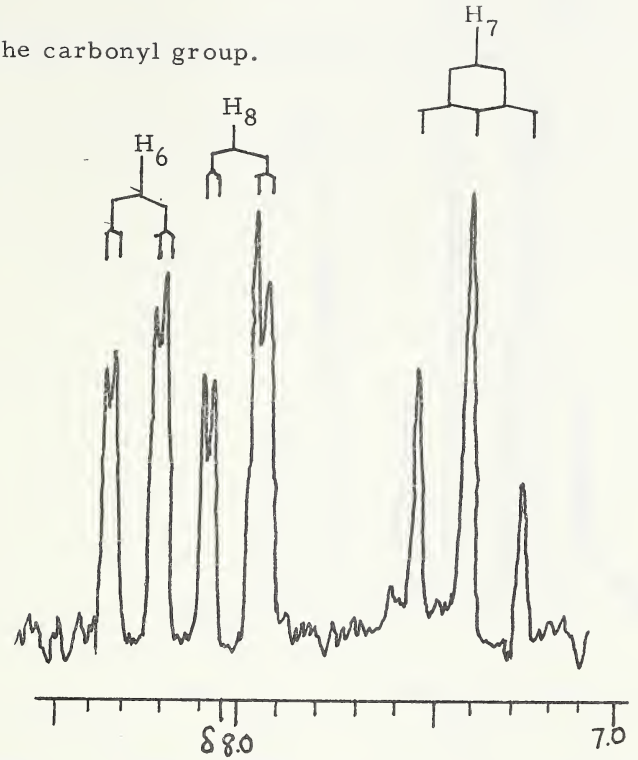
Nakamura (1940) reported that oxidation of 5-nitrotetralin with chromic anhydride resulted in a 20% yield of a mixture of the 5- and 8-nitro compound, 80 and 95 ; the isomeric ratio of the 5- and 8-nitro compounds was 3:1. Repetition of the above procedure under the same reaction condition, gave the same mixture in a yield of 8.4%. The poor yield of this reaction is conceivable since the nitro group

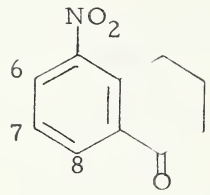
would be expected to strongly deactivate the oxidation reaction. Fractional crystallization of the product first gave 5-nitro-1-tetralone m.p. 98-102°. The residue was irresolvable upon further crystallization and thus it was subjected to column chromatography on alumina. The three isomers came out in the following order: The first fraction had a m.p. of 98-102° and was identified as 5-nitro-1-tetralone. The second fraction was found to be 6-nitro-1-tetralone (m.p. 102-104°) and the third, 8-nitro-1-tetralone (m.p. 147-150°).

7-Nitro-1-tetralone melted at 104-105° (Schroeter gave m.p. 106°); this depressed the m.p. of the isomer from fraction 2 to 74-85°, which must be the 6-nitro-1-tetralone. The depression in mixed m.p. was also observed for the first and second fraction (m.p. 65-80°).

The structural elucidation of these positional isomers was aided by their PMR data. The aromatic signals of each isomer displayed a characteristic splitting pattern dependent on the position of the nitro group. 5-Nitro-1-tetralone (80) had H_7 ortho coupled to both H_6 and H_8 (J = 8 Hz), and a triplet resulted. H_6 and H_8 each formed a doublet of doublets arising from one ortho and one meta coupling (J_{ortho} = 8 Hz, J_{meta} = 1.5 Hz). The aromatic signals of the 6- and 8-nitro isomers were quite different; that of the 8-nitro derivative showed an irresolvable pattern and that of the 6-nitro compound gave a broad singlet. This observation shows that chemical shift differences between H_5, H_7 and H_8 are small. H_5 and H_7 are deshielded by the nitro group to the same extent as is H_8

by the carbonyl group.



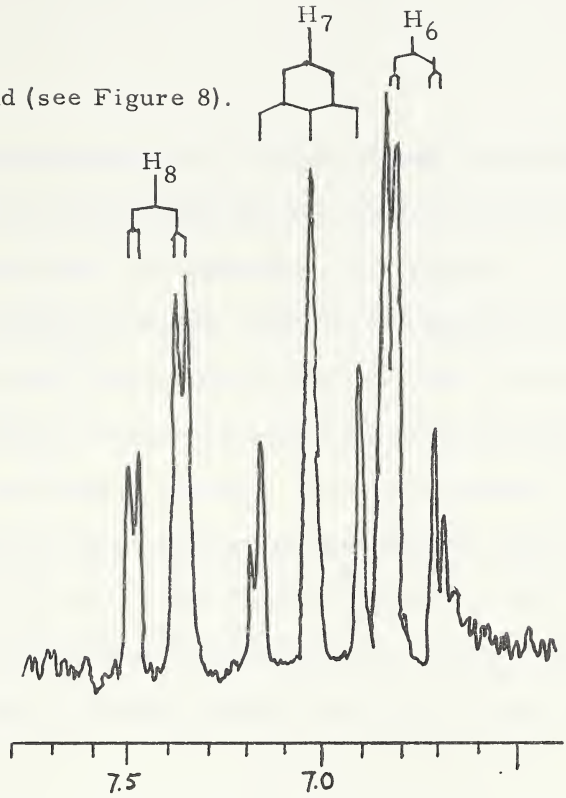


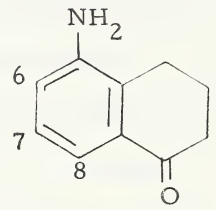
(80)

Figure 7 Part of PMR spectrum of 5-nitro-1-tetralone recorded at 60 MHz in $CDCl_3$.

Reduction of the 5-nitro compound 80 by a literature method (Nakamura, 1940) with stannous chloride and hydrochloric acid yielded compound 99. The IR spectrum of this compound displayed two bands at 3410 and 3340 cm^{-1}, typical of asymmetric and symmetric NH stretching of a primary amine. The nitro absorption band which was present in the starting material at 1530 cm^{-1}, disappeared. In the PMR spectrum of 5-amino-1-tetralone (99), an upfield shift of all aromatic signals can be noted relative to those of the nitro analog. This is due to removal of the deshielding effect of the nitro group. The amino group through its positive mesomeric effect shifts H_6 to

the higher field (see Figure 8).





(99)

Figure 8 Part of PMR spectrum of 5-amino-1-tetralone (99) at 60 MHz in $CDCl_3$.

Attempted Synthesis of 5-Dimethylamino-1-tetralone Methiodide (102)

Initially, the procedure for synthesizing 6-dimethylamino-1-tetralone methiodide (77) was employed in an attempt to prepare compound 100. Treatment of 5-amino-1-tetralone (99) with excess of methyl iodide, however, invariably gave a dark brown product which could not be resolved. Alteration of the reaction conditions and solvent was to no avail. Dimethyl sulfate was also used as a methylating agent, but this too failed to methylate the primary amine. Purification of the gummy product with active charcoal did not afford any improvement. The product gave a negative reaction with

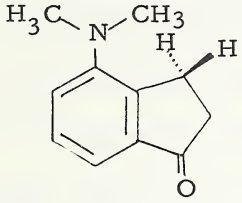
2,4-dinitrophenylhydrazine (2,4-DNP) reagent for the identification of a ketone. This test indicated that the starting material was unstable and decomposed under the condition of methylation.

Use of milder reaction condition as reported by Sommer and Jackson (1970) was investigated without success. The reaction involved stirring an aromatic primary amine with methyl iodide and 2,6-lutidine in a suitable solvent. Since 2,6-lutidine is a stronger base than most anilines, and its nitrogen atom is sterically hindered, it only acts as a base to take up the hydrohalide. But it does not methylate. 2,6-Lutidine hydrohalides are usually freely soluble in the solvent, thus the methyl iodide of the amine under study usually precipitates.

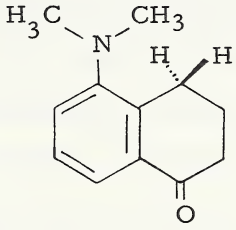
Steric Factors in Methylation of 5-Amino-1-tetralone (99)

Since various methylation procedures gave negative result, it was considered that the methylene group ortho to 5-amino group might sterically retard the S_N2 type replacement on the nitrogen atom of the amine 99. Thus, reductive methylation of 5-nitro-1-tetralone using formaldehyde and 10% Pd/C as catalyst, (Ingram, 1950) was applied. The result was successful and 5-dimethylamino-1-tetralone was obtained in a yield of approximately 70%. However, this tertiary amine could not be methylated with methyl iodide even upon heating in a sealed tube at 120° for 5 hr; only the starting base was recovered.

To test the ideas of steric retardation of methylation, 4-dimethylamino-1-indanone (142) was made later.



142



96

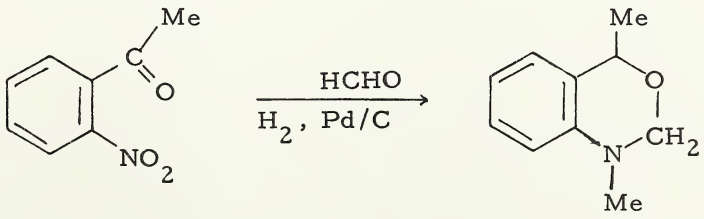
According to the Dreiding models of the two molecules, the indanone compound 142 has its two hydrogen atoms remote from the amino group and should be methylated with ease because it is free from steric hindrance; when this compound was stirred with methyl iodide in acetone at room temperature the corresponding quaternary ammonium salt resulted. In conclusion, the failure to methylate 5-amino-1-tetralone to any degree was probably due to a steric hindrance factor.

An N-methyl quaternary salt of the tertiary base 96 was finally made by fusion of the base 96 with methyl tosylate on a steam bath for four days; the tosylate salt 97 resulted. The tosyl group is known to be a better leaving group than iodide (Fieser and Fieser, 1961) and this factor may be responsible for the formation of the product. Treatment of the tosylate salt with hydrazine yielded the corresponding hydrazone 98. The aromatic signals of the PMR spectra of these two compounds could not be resolved.

Attempted Synthesis of 8-Dimethylamino-1-tetralone Hydrazone Methiodide (103)

Reduction of 8-nitro-1-tetralone by a similar procedure to that described for the preparation of 5-amino-1-tetralone (99) gave the corresponding 8-amino compound (101). Methylation of the compound 101 with methyl iodide/sodium carbonate failed to provide the quaternary ammonium salt 102; steric hindrance or electron withdrawing effect of the C=O group which reduces the basicity of the amine group may again account for the failure of the reaction. Since the amount of 8-amino-1-tetralone (101) was limited, further studies could not be carried out.

Instead, o-nitroacetophenone was examined as a model for testing the reductive methylation procedure. It was planned that if o-nitroacetophenone could be successfully converted to o-dimethylaminoacetophenone, more 8-nitro-1-tetralone (95) would be made and subjected to the same reaction. In fact, cyclization took place when o-nitroacetophenone was allowed to react with hydrogen in the presence of formaldehyde and a Pd/C catalyst. 1,4-Dimethyl-4H-[3,1]-benzoxazine(104)formed (see the reaction below). The proof

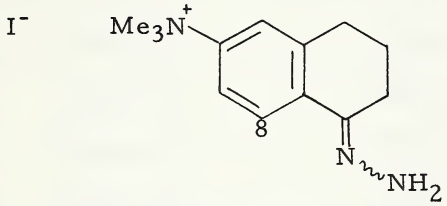


104

of this structure follows. The IR spectrum of the compound showed no carbonyl stretching band, indicating the loss of the carbonyl group The PMR spectrum gave a secondary methyl signal at δ 1.43 (J = 6.5 Hz) and a methyl singlet (NMe) at δ 2.77. Moreover, a lower field singlet at δ 4.52 (2 protons) was noted; the low field chemical shift of the methylene group indicated the deshielding effects of both the adjacent oxygen and nitrogen atom.

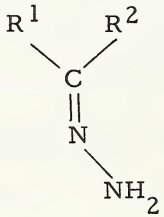
CONFIGURATIONAL STUDIES OF HYDRAZONES

A possible approach to gaining information about the configuration of the 1-hydrazone substitution of 6-dimethylamino-1-tetralone hydrazone methiodide 78 is a study of the chemical shift of the protons



78

at C_8. It has been reported that in hydrazones 105 , the PMR signal of α-CH_2 syn to the NH_2 function resonates at lower field than the



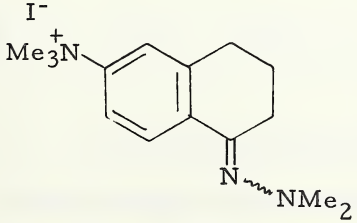
105 R^1, R^2 = alkyl

corresponding anti α-CH_2 protons (Karabatsos and Osborne, 1968). The chemical shift data of some isomeric hydrazones are summarized in the following table.

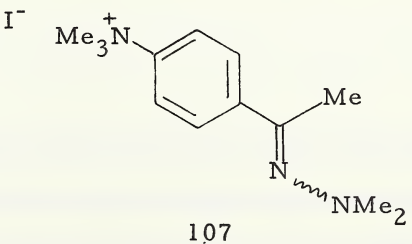
Table 7 Chemical Shifts (δ) of Hydrazones

$R^1R^2C=NNH_2$		Solvent	H_α (CH_2)	
R^1	R^2		syn	anti
H	$CH_2C_6H_5$	CCl_4	3.65	3.45
CH_3	CH_2CH_3	neat	2.16	2.13
CH_3	$CH_2C_6H_5$	CCl_4	3.45	3.39
CH_3	$CH_2C_6H_5$	C_6H_6	3.16	3.12

Unfortunately, the PMR signals of the protons that would have been of configurational value in the present case could not be resolved, and a six-proton multiplet (δ 2.36) was observed in the PMR spectrum of compound 78 . Moreover only one member of the geometrically isomeric pair was obtained and it would not have been possible to make comparisons between the two isomers. Attention was then directed to studies of the N,N-dimethylhydrazone derivatives of the ketones, e.g. 106 and 107. It may be argued that since the NH_2 and



106

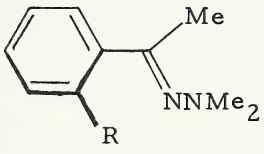


107

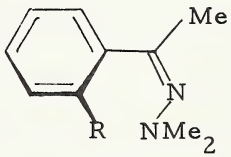
NMe_2 groups are not too dissimilar, the configurational preference of these two groups are likely to be the same. Newkome and Bhacca

(1971) reported that the PMR spectra of the ortho-substituted acetophenone N,N-dimethyl hydrazones (108) displayed duplicate CMe and NMe singlets while those of the unsubstituted hydrazones (R = H) only showed single C- and NMe singlets. The chemical shifts of the methyl protons of some isomeric hydrazones are given below.

Table 8 PMR Chemical Shifts (δ) for Methyl Protons



anti



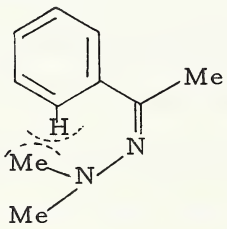
syn

108

	anti isomer		isomer ratio		syn isomer	
R	CMe	NMe	anti	syn	CMe	NMe
OMe	2.25	2.51	60	40	2.10	2.28
Me	2.31	2.50	53	47	2.08	2.28
Br	2.24	2.52	57	43	2.15	2.31
Cl	2.28	2.51	68	32	2.15	2.25
H	2.26	2.50	100			

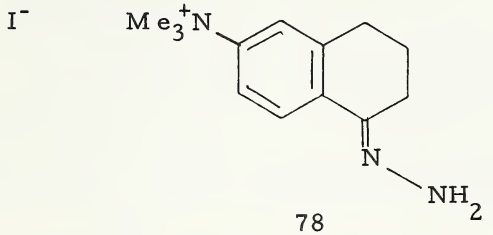
The NMe_2 protons of the syn isomers are in close proximity to the aromatic ring and are subjected to the strong ring shielding effect. Hence the NMe_2 proton signals at lower field of the PMR spectra are assigned to the anti isomers and that at higher field to the syn isomers. In the absence of ortho substituents the acetyl

group of acetophenone is coplanar with the aromatic ring, and the hydrazones derived from this ketone adopts the anti configuration as judged from the NMe chemical shift. Steric hindrance between the NMe_2 group and the phenyl ring is not likely in the anti configuration; thus the coplanarity of double bond and phenyl ring may give rise to significant resonance stabilization, which, in turn leads to the anti isomer as the sole product in the unsubstituted acetophenone. The chemical shift of NMe_2 protons of the unsubstituted hydrazone (108 R = H) and the anti isomer of the ortho-substituted are found to be comparable. The presence of ortho-substituents induces twisting of the acetyl group from the plane of the aromatic ring. The deviation of the acetyl group from coplanarity existing in ketones as well as in



N,N-dimethylhydrazones reduces the proximate steric crowding by the ortho-substituent, and allows the N,N-dimethylhydrazones to exist in both syn- and anti-configuration as in N,N-dimethylhydrazones of simple alkyl ketones (Karabotsos and Taller, 1968). As anticipated the PMR spectrum of compound 107 showed NMe_2 and CMe singlets at δ 2.47 and 2.72 respectively; that of the compound 106 exhibited an NMe_2 singlet at δ 2.58. No duplication of the methyl signals in the PMR spectra of compounds 106 and 107 was observed. In addition, the chemical shift value indicated that the anti isomers were

the only ones obtained in the reaction. Extending the argument to the desmethyl derivatives, it was possible to designate the anti as the probable configuration for compound 78 and its analogs.



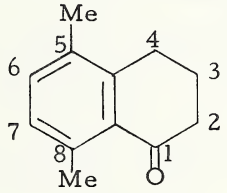
78

The synthesis of compounds 106 and 107 was not without problems. Refluxing p-dimethylaminoacetophenone methiodide with unsym-N,N-dimethylhydrazine led to the isolation of a white solid, which was identified as N,N,N-trimethylhydrazinium iodide 109. The m.p. of the white solid was found to be 214-217°, while the m.p. of authentic N,N,N-trimethylhydrazinium iodide prepared by a reaction of methyl iodide with hydrazine was 223-225° (Merck Index, 1968, gave 223-225°); the mixed m.p. was found to be 218-222°. The PMR spectra of 109 and the authentic sample of N,N,N-trimethylhydrazinium iodide were superimposable, with the N^+Me_3 protons coming to resonance at δ 3.30 and the NH_2 protons at δ 6.18.

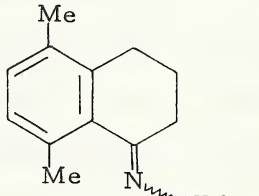
In a literature survey, it was found that the use of acetic acid as catalyst facilitated hydrazone formation (Szmart, 1950). Thus, glacial acetic acid was employed in the present case. A mixture of equal molar quantities of the hydrazine, glacial acetic acid and p-dimethylaminoacetophenone methiodide in ethanol was heated under reflux for 3 hr. On cooling the desired product precipitated; its

PMR features confirmed its structure. The PMR spectrum of 106 displayed three singlets at δ 2.47, 2.72 and 3.83 arising from CMe, NMe_2 and N^+Me_3 respectively. The aromatic protons of 106 appeared as a broad singlet at δ 8.02.

To secure further evidence of the anti disposition of the phenyl ring and the NMe_2 group, 5,8-dimethyl-1-tetralone (110) was prepared. It was considered that the Me group at C_8 would disturb the coplanarity



110



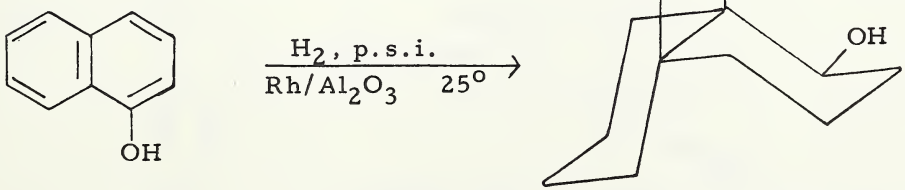
111

between the carbonyl and the phenyl ring, and that the N,N-dimethylhydrazones derived from this ketone would be likely to exist as syn and anti isomers. The preparation of compound 110 followed a literature procedure without any difficulty (Kadyrov and Lainapov, 1966). However, attempts to prepare the N,N-dimethylhydrazone met with no success. Various reaction conditions were tried including heating the ketone 110 with unsym-N,N-dimethylhydrazine in a sealed reaction flask at 140° for 5 to 6 hr. The unreacted ketone 110 was recovered. The failure to synthesize this compound may be ascribed to the steric hindrance caused by the C_8-Me group.

HYDROGENATION STUDIES OF 6-DIMETHYLAMINO-1-TETRALONE HYDRAZONE METHIODIDE

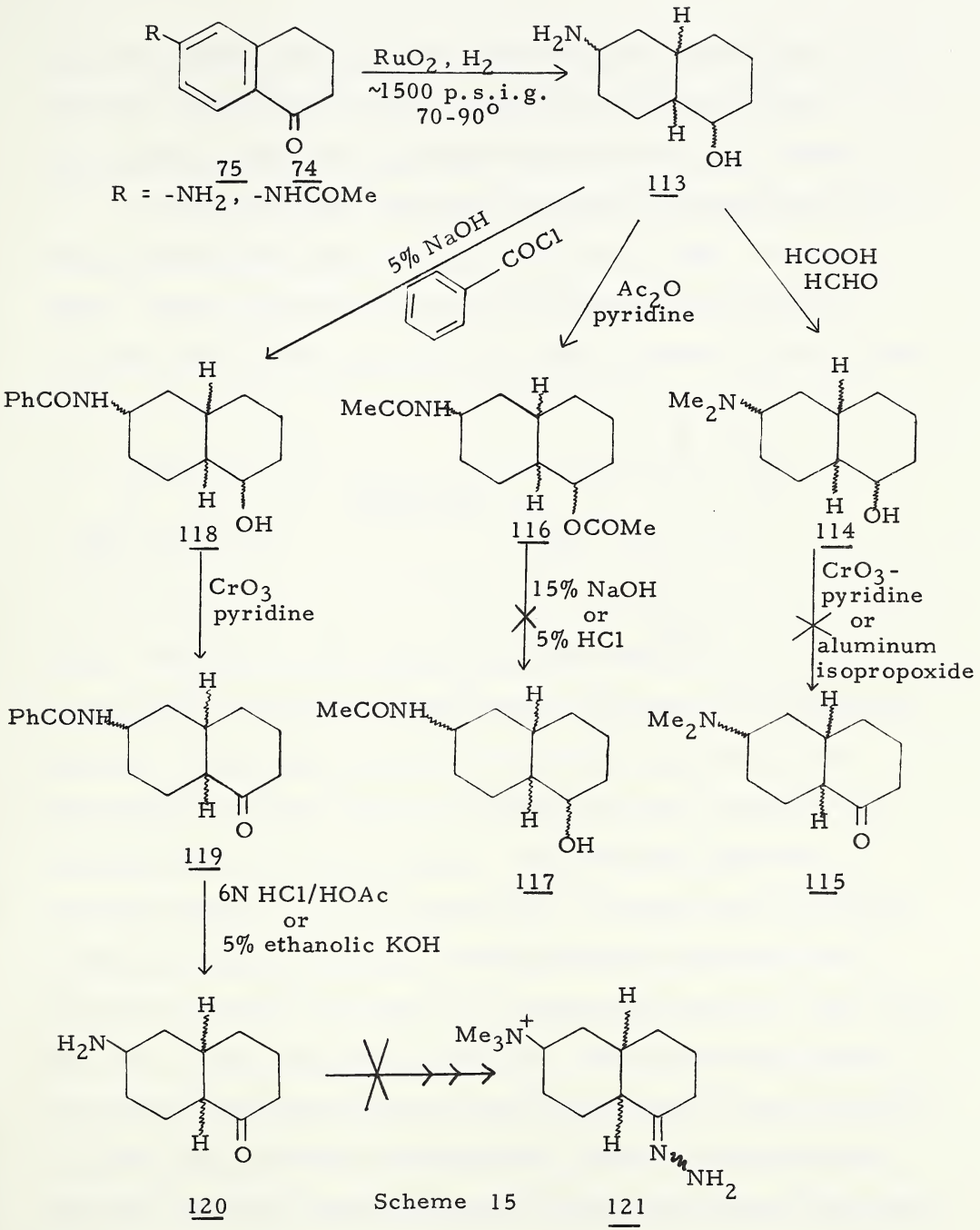
6-Dimethylamino-1-decalone hydrazone methiodide (121) may be considered as a hydrogenated counterpart of 6-dimethylamino-1-tetralone hydrazone methiodide (78). Thus, it can be synthesized by a procedure similar to that described for 78 provided that the aromatic ring is hydrogenated at a suitable stage. The following scheme shows the proposed synthetic route for this compound.

Hydrogenation of the aromatic ring may be accomplished by platinum or Raney nickel catalyst but these catalysts also induce isomerization and hydrogenolysis of alcohols of benzylic type (Augustine, 1965). In the present investigation, a benzylic alcohol is likely formed as an intermediate and hence is susceptible to undesirable hydrogenolysis. To avoid these complications 5% rhodium on alumina and ruthenium catalysts were chosen. Meyers et al. (1964) reported the advantages of rhodium catalyzed reduction. Under very mild condition α-naphthol could be reduced to cis, cis-1-decalol 122 as major isomer, and the hydrogenolysis was found to be only 3%



62%

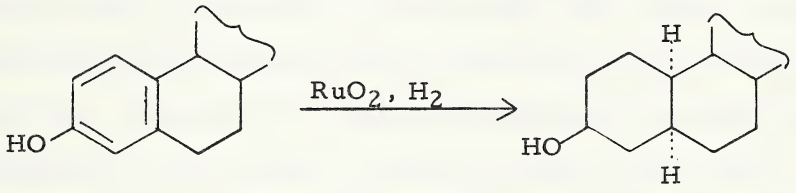
122


R
RuO_2, H_2
~1500 p.s.i.g.
70-90°
H_2N
H
OH
O
75
74
R = -NH_2, -NHCOMe
113
5% NaOH
COCl
Ac_2O
pyridine
HCOOH
HCHO
PhCONH
MeCONH
Me_2N
118
116
OCOMe
114
CrO_3
pyridine
15% NaOH
or
5% HCl
CrO_3-
pyridine
or
aluminum
isopropoxide
119
117
115
6N HCl/HOAc
or
5% ethanolic KOH
Me_3N^+
N
NH_2
120
121

Scheme 15

(the stereochemistry of this compound will be discussed later). In contrast, a 48% yield and 8% hydrogenolysis resulted from the hydrogenation catalyzed by platinum oxide (Dauben et al., 1954).

A stereoselective reduction of steroids by rhuthenium was demonstrated by the others (Rapala and Farkas, 1958; Counsell, 1961). It thus appeared that the use of rhodium and ruthenium catalysts offered advantages over Pt in hydrogenation reactions of this



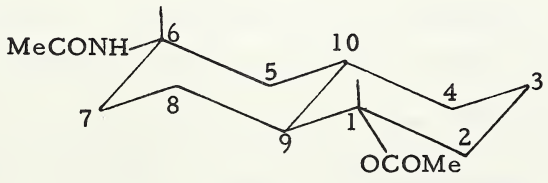
123

class. Therefore, a low pressure hydrogenation (68 p.s.i.) of 6-acetamido-1-tetralone with 5% rhodium on alumina was attempted. However, no hydrogen absorption occurred for a period of 24 hr. The rhodium catalyst, which successfully reduced 1-naphthol, was not applicable in the present case. Meanwhile the application of ruthenium dioxide was also investigated. A mixture of 6-acetamido-1-tetralone (74) and ruthenium dioxide in ethanol was shaken in an autoclave at 70-90° and 1480 p.s.i. of hydrogen pressure. The reduction was usually completed in 6 to 7 hr. The product was found to be soluble in 5% hydrochloric acid and was therefore a basic material. A purification procedure was undertaken, and it involved dissolving the basic material in 5% hydrochloric acid and subsequently liberating the free base with 5% aqueous sodium hydroxide. Deacetylation

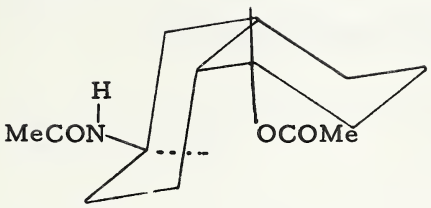
possibly took place and gave rise to the product as 6-amino-1-decalol. The IR spectroscopic evidence suggested that a primary amino-alcohol was obtained as the spectrum showed an absorption band at 3600 cm^{-1} (OH) and a broad band between 3400-3000 cm^{-1} (H-bonded OH and NH). 6-Amino-1-tetralone (75) was used in the hydrogenation studies, and was reduced in a manner similar to that described for 6-acetamido-1-tetralone. The reduced product, 6-amino-1-decalol (113) did not form a solid on attempted crystallization from various solvents. The hydrochloride and hydrobromide salts were too hygroscopic to be purified. Therefore, the characterization and configurational assignment of the product could not be made at this stage. The IR spectrum of the product showed the characteristics identical to that of the basic material already assigned as 6-amino-1-decalol (113). The mass spectrum of the crude oil displayed a peak at m/e 169 (rel. abundance 9%) corresponding to the molecular weight of 6-amino-1-decalol (113). The PMR spectrum showed a broad signal at δ2.72 which integrated for three protons (NH_2 and OH protons), and disappeared after deuteration. All spectroscopic data confirmed that 113 was the correct structure of the reduced product, and it was used for the subsequent synthesis without purification. Further information on purity was obtained by thin layer chromatography (TLC). Thus, compound 113 was spotted on a thin layer plate (MN-Kieselgel G 0516), dried and developed in a tank filled with a 1:1 mixture of chloroform and methanol in an ascending manner. The chromatogram showed four spots with different Rf values as calculated from the

distance travelled by the solvent and each component (Rf 0, 0.24, 0.32 and 0.65). This result suggested that at least four components were present in the reduced product. Leov and Goodman (1967) reported that a direct relationship could be found between TLC and "dry-column" chromatography. The conditions such as adsorbant and solvent systems which achieved separation in the former could be successfully transferred to the latter for a preparative scale. The dry-column chromatography technique involved dry packing the adsorbant, followed by addition of the compound to be resolved on the top of the column. Elution was stopped as the eluting solvent reached the bottom of the column and the separation was called complete. Extraction of the different fractions of the adsorbant afforded recovery of the resolved components. Unfortunately, this technique failed to resolve 113 in the present investigation. It was then considered that crude 6-amino-1-decalol (113) could be used to form 6-dimethylamino-1-decalol (114) which could be subsequently oxidized to the ketone, namely 6-dimethylamino-1-decalone (115). Thus, crude 6-dimethylamino-1-decalol (114) was prepared from 6-amino-1-decalol (113) by the Leuckart reaction. Vacuum distillation did not appear to purify the compound. Salt formation did not afford crystalline material. Although an analytical sample of 114 could not be obtained, the PMR spectrum of the base did show two NMe signals near δ2.40, characteristic of the chemical shift of the NMe resonance (Jackman and Sternhell, 1969). Compound 115 was then oxidized using i) chromic anhydride-pyridine or ii) aluminum isopropoxide. It was found that

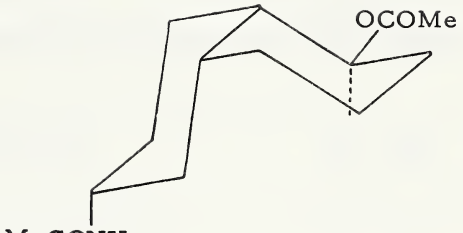
the former decomposed the compound as the oxidized material did not show any NMe PMR signal. The latter reagent did not effect complete oxidation; the IR spectrum of the product exhibited a weak ketone absorption band at 1700 cm^{-1} but a strong hydroxyl stretching band at 3400 cm^{-1}. This synthetic route was then abandoned. The results indicated that the tertiary amino compound 114 was unstable to oxidation and a protecting group was required. The acetyl group was first considered and acetyl chloride was chosen as acetylating agent. However, the acetylated product was found to be difficult to purify. Acetic anhydride was employed as an alternative. Treatment of 113 with acetic anhydride and pyridine at room temperature resulted in a diacetyl derivative at N and O atom (116). Recrystallization of 116 gave a crystal (m.p. 139-141°). Other isomers obtained from the catalytic hydrogenation and subsequent acetylation might be present in the acetylation product but the major one isolated was 116. The elemental analysis also supported the structure of 116. The IR spectrum displayed two absorption bands at 1740 and 1650 cm^{-1} characteristic of an ester and amide respectively. The configuration of 116 was tentatively assigned on the basis of PMR evidence. The PMR spectrum showed two separated signals at δ4.92 and 3.88.



116a



116b

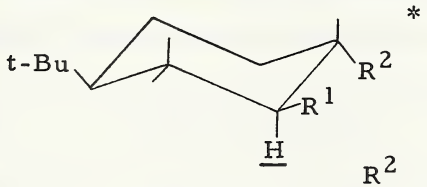
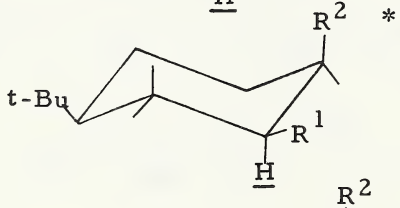
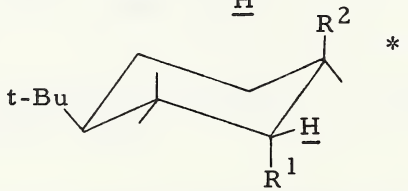


116c

The Probable Configurations of 116

The multiplet at the lower field position (δ4.92) was assigned to H_1 based on the stronger deshielding effect of an oxygen atom, and that of the higher field position (δ3.88) to H_6 adjacent to a nitrogen atom. The H_1 signal of 113 appeared as a multiplet at δ3.50 (the dimension of the signal width at half height ($W\frac{1}{2}$) of this proton could not be measured due to the presence of impurities). An acylation shift from δ3.50 to δ4.92 was also noted for this proton when was converted to its acetate derivatives 116 (Culvenor, 1966). Since H_1 is not coupled to any exchangeable proton its $W\frac{1}{2}$ should not be altered after deuteration of 116 with D_2O. Indeed the $W\frac{1}{2}$ of H_1 remained the same after deuteration. In contrast, the resonance signal of H_6 at δ3.88 was narrowed from 20 Hz to 16.5 Hz, and the doublet due to NH resonance at δ6.34 (J=7 Hz) disappeared after this treatment. The configurational assignment was made based on $W\frac{1}{2}$ of H_1 and H_6 as compared to that of other methine signals of which the stereochemistry is known. The dimensions of the $W\frac{1}{2}$ of some model compounds are given in the following table:

Table 9 Dimensional Parameters of Methine PMR Signals from Spectra of Model Compounds and Compounds Under Study.

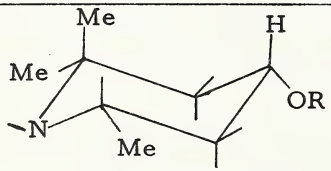
Type of Coupling ^3J	Compounds	$W\frac{1}{2}$ (Hz)
2aa, 1ae	 *	21, 19.5, 21.5 21, 24, 20, 21 21.5
1aa, 2ae	 *	18, 19, 18.5
2ee, 1ea	 *	6.5, 7.0, 8.0, 6.0
1aa, 2ae (H_1)	6-Acetamido-1-acetoxy-decalin (116)	13.5
1aa, 2ae (H_1)	cis,cis-1-decalol (122)	16

* From Casy et al. (1972), R^1 = NH_2, NMe_2, R^2 = OH, OCOMe.

The magnitude of $W\frac{1}{2}$ of H_1 in 116 is 13.5 Hz; this value is too small for 2aa, 1ae coupling, and also too large for 2ee, 1ea coupling. Therefore, it is reasonable to assume that the $W\frac{1}{2}$ of H_1 is derived from 1aa, 2ae case where the proton is axially disposed in configuration 116b. The disposition of H_6 is designated in a similar manner. The

dimension of $W\frac{1}{2}$, base width (bw) and base width measured from the separation of two outer lines (bw*) of H_6 are used. The parameters from the model compounds and 118 are given in table 10.

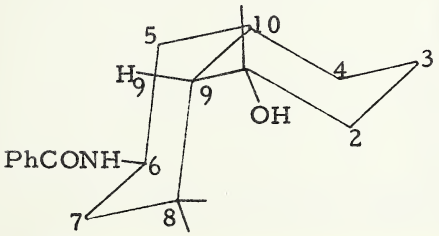
Table 10 Dimensional Parameters of Methine Signals from Spectra of Model Compounds and Compounds Under Study.

Type of Coupling ^3J	Model Compounds	$W\frac{1}{2}$	bw	bw*
2aa, 2ae	 *	20		32.4
2aa, 2ae (H_6)	6-acetamido-1-acetoxy-decalin (116)	16.5	32	
2aa, 2ae (H_6)	6-benzamido-1-decalone (118)	22		32.5

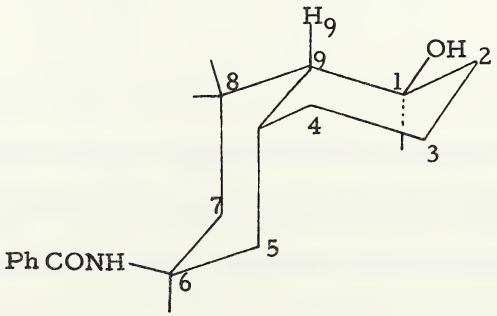
* From Casy et al. (1972), R=Ph

It can be noted that these figures are quite comparable, and suggests that H_6 is axially oriented. This configurational assignment is in agreement with the stereochemistry of catalytic hydrogenation, which usually induces a cis addition of hydrogen to one side of the molecule to be reduced. The fact that H_1 was consisted of 2ae and 1aa coupling and that H_6 was consisted of 2aa and 2ae coupling ruled out 116a and

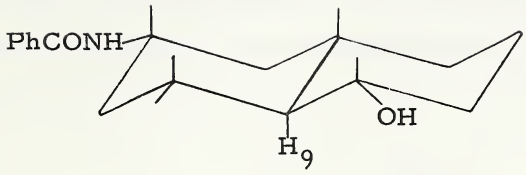
116c as the possible configurations, and it appeared that 116b was the only probable configuration for 116. Attempts to hydrolyze selectively the ester function of 116 with aqueous sodium hydroxide failed. The amide function could not be retained intact if complete hydrolysis of the ester was desired. Thus, an acylating agent which could selectively protect the amino group by amide formation and at the same time allow the hydroxyl group to be available for oxidation, was required. Benzoyl chloride was employed in the hope that it could fulfill these requirements. When a mixture of 113 and benzoyl chloride was allowed to react under controlled conditions, only the N function was acylated as hoped and 6-benzamido-1-decalol 118 formed. The method of configurational assignment of 118 was slightly different from that of 116 described above. Use was made of the splitting pattern of H_9 for the configurational assignment at the bridgehead. In DMSO-d_6



118a

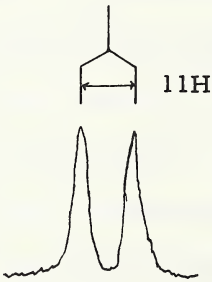


118b



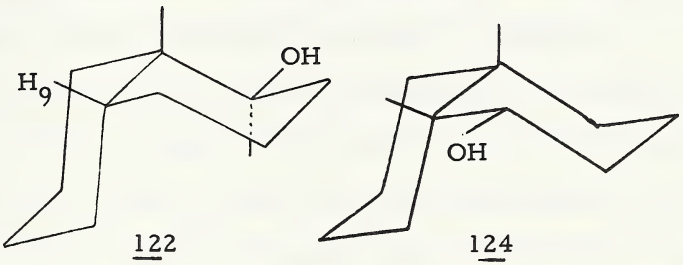
118c

H_9 was not resolved. When pyridine-d_5 was employed as solvent this bridgehead proton was shifted downfield and became separated from the rest of the ring protons. The deshielding phenomenon is attributed to the anisotropic effect of the pyridine ring, which is associated with the solute through hydrogen bonding (Demarco, 1968). The H_9 was coupled, with a large Jaa value (11 Hz) to a doublet which was further split with 3 Jee couplings into a pair of humps as shown below. This argument ruled out 118c , but it did not indicate which



of the remaining two isomers (118a or 118b) was the possible configurational isomer. The $W\frac{1}{2}$ of H_6 (22 Hz) was very close to those of models compounds (20 Hz, Table 10), suggested that this proton was axially disposed.

To confirm the configurational assignment of 118, cis,cis-1-decalol (122) was synthesized. The configuration of this compound was already established by both chemical and spectroscopic methods



122 124

(Dauben et al., 1951; Grob and Tam, 1965). Using the Tschugaeff elimination reaction, a cis,cis-configuration was assigned for the decalol 122 (Dauben et al., 1954). We synthesized 122, and recorded its PMR spectra in pyridine-d_5 at 100 MHz and 220 MHz. The PMR spectrum of 122 did not show a pair of singlets for H_9 at the desired region as did 118. Thus, it appeared that probably 118 and 122 did not have the same configuration at the bridgehead. Since cis,cis-1-decalol was not the desired reference compound, perhaps cis,trans-1-decalol (124) would be a better model. An attempt to make 124 by the procedure of Grob and Tam (1965) was carried out. However, the isolation of cis,trans-1-decalol from the rest of the isomers using a gas chromatographic method was not successful, and this was not further investigated.

The oxidation of 118 was effected by chromic anhydride-pyridine complex and afforded 6-benzamido-1-decalone (119) in 40% yield. The IR spectrum of 119 showed an absorption band at 1700 cm^{-1}

characteristic of a ketone of cyclohexyl ring. The axial orientation of H_6 in this compound was unambiguously indicated by the bw* of this proton, whose value was close to those of the reference compounds (see Table 10). It was probable that no change in configuration at the ring junction took place during the process of oxidation.

Hydrolysis of 119 met unexpected difficulties. An attempt to hydrolyze the amide in a mixture of the equal amount of hydrochloric acid and glacial acetic acid resulted in the starting material, as the IR spectrum showed an amide absorption band at 1633 cm^{-1}. Base catalyzed hydrolysis was not successful either. 5% ethanolic potassium hydroxide caused decomposition of the ketone function before it cleaved the amide group; the IR spectrum of the hydrolyzed product retained the amide but not the ketone absorption band.

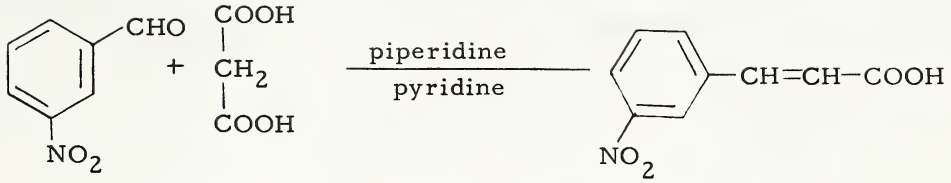
Finally, it was concluded that a protecting group, such as formamido, which could be removed under mild conditions and yet affords a reasonable protective effect for the amino function was required. Due to the limited supply of 6-amino-1-decalol 113, the problem could not be further investigated. Therefore, the synthesis of the final product 6-dimethylamino-1-decalone hydrazine methiodide (121) was not achieved.

SYNTHESIS OF AMINOINDANONE HYDRAZONE METHIODIDES

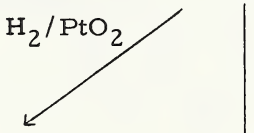
5-Dimethylamino-1-indanone Hydrazone Methiodide (135) and 7-Acetamido-1-indanone (131)

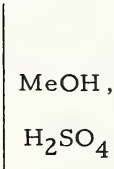
Compound 135 may be considered as a five member ring analog of the tetralone 78, and hence 5-amino-1-indanone (132) is the required intermediate. It has been discussed before that an appropriately substituted phenylbutyric acid can be cyclized to a desired tetralone. By the same token a suitably substituted phenylpropionic acid (hydrocinnamic acid) may form an indanone by ring closure. Thus, m-acetamidohydrocinnamic acid (129) should afford both 5-acetamido-1-indanone (130) and 7-acetamido-1-indanone (131) upon intramolecular cyclization. Various methods were sought to make the compound 129. The scheme of synthesis for compounds 129 and then 135 and 131 is presented below (Scheme 16).

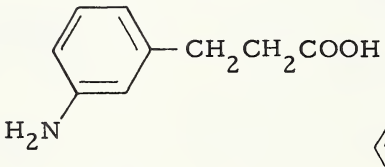
Cinnamic acid may be prepared by condensing benzaldehyde with acetic acid, its esters or anhydrides. Reactions such as the Perkin, Reformatsky, Claisen and Knoevenagal all give this compound in approximately 60-80% yield (Shriner, 1942). Substituted cinnamic acids can also be prepared successfully by these reactions. In the present investigation, a Doebner modification (Schriner, 1942) of the Knoevenagal reaction was employed, which involved the use of pyridine in place of an aliphatic tertiary amine as a base catalyst. Thus, a mixture of 3-nitrobenzaldehyde, pyridine, piperidine and malonic acid was heated on a steam bath, and m-nitrocinnamic acid (125)



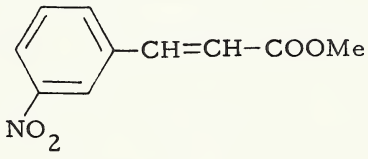
125



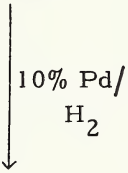


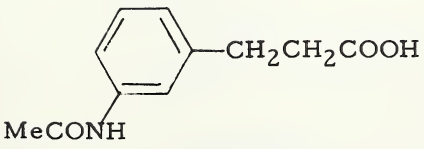


136

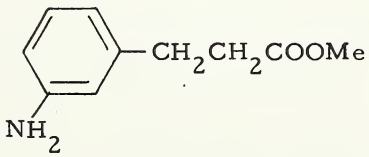


126





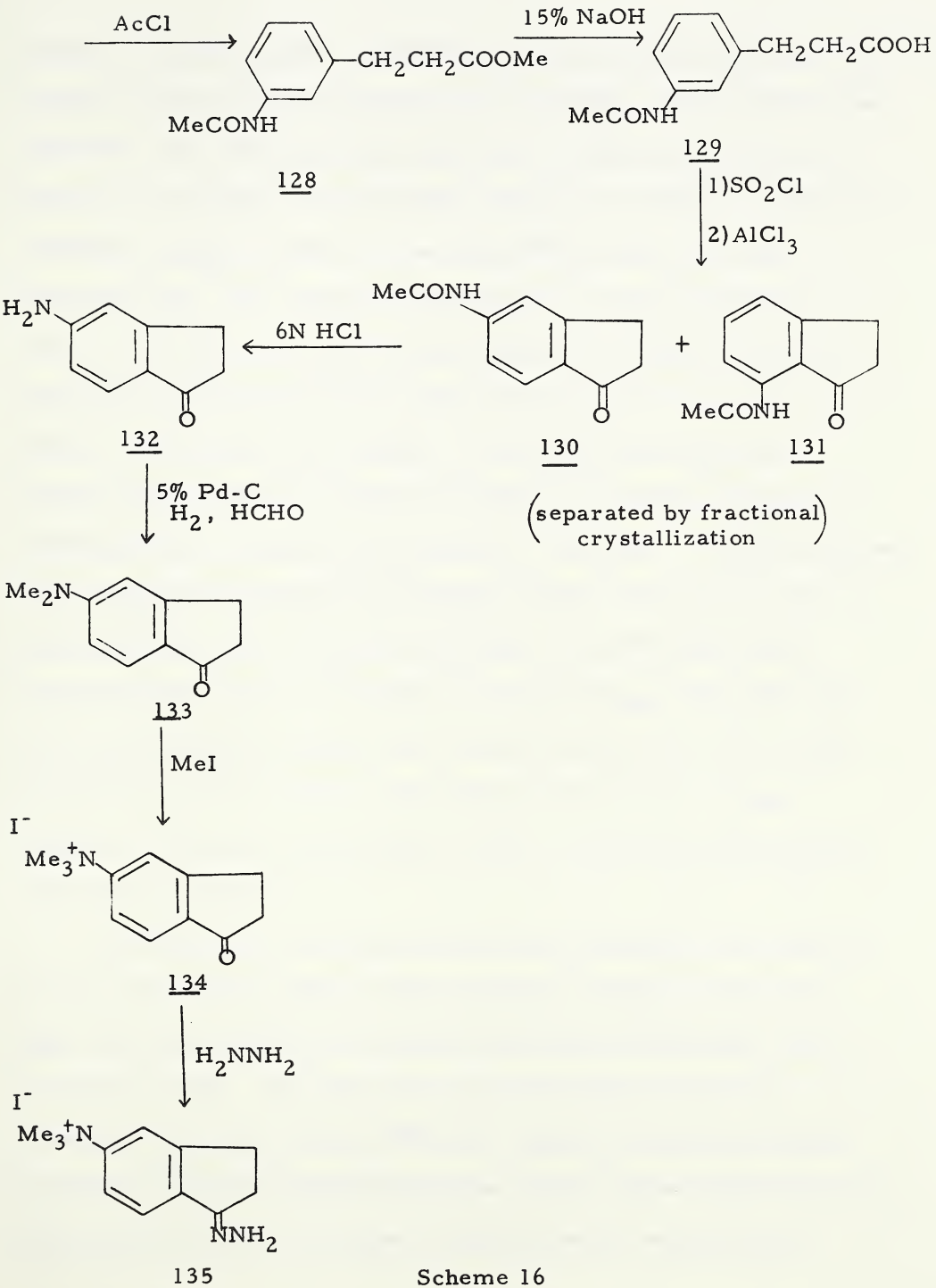
129



127

Scheme 16

Continued . . .


AcCl
CH2CH2COOMe
MeCONH
128
15% NaOH
CH2CH2COOH
MeCONH
129
1) SO2Cl
2) AlCl3
MeCONH
+
MeCONH
130
131
(separated by fractional crystallization)
6N HCl
H2N
132
5% Pd-C
H2, HCHO
Me2N
133
MeI
I-
Me3+N
134
H2NNH2
I-
Me3+N
NNH2
135

Scheme 16

formed in excellent yield. Initially, it was planned to reduce m-nitrocinnamic acid to m-aminohydrocinnamic acid (136), which could be then acetylated and cyclized to form the desired substituted indanones. However, it was later found that the acid 136 was difficult to purify and acetylation of 136 resulted in a low yield (39%) of the acetamido derivative 129. Due to these disadvantages, it was considered desirable to convert the acid functional group of compound 125 to its methyl ester during the process of purification and acetylation. Indeed, this operation was fruitful. The methyl ester 126 was synthesized in excellent yield by refluxing the acid 125 in methanol containing a few drops of sulfuric acid as catalyst. The IR spectrum of the compound displayed an absorption band at 1730 cm^{-1}, characteristic of an ester carbonyl stretching. The PMR spectrum showed that the aromatic and ester group were trans with reference to the carbon-carbon double bond because the J value of the vinylic proton at δ 6.59 was 16 Hz, which falls into the range of trans coupling. (Jackman and Sternhell, 1969). The other vinylic proton could not be resolved.

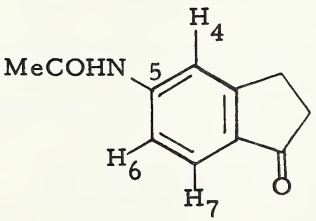
Hydrogenation of methyl m-nitrocinnamate (126) at atmospheric pressure proceeded rapidly to give methyl m-aminohydrocinnamate (127). The compound 127 was purified by vacuum distillation, and the yield was 91%. The IR spectrum of the compound had two absorption bands at 3460 and 3380 cm^{-1} typical of a primary amine. The PMR spectrum established that the carbon-carbon double bond was hydrogenated because the signal of vinylic protons was no longer

present. A general upfield shift of the aromatic signal (δ 6.65 vs. δ 7.62) was observed, as a result of the removal of the deshielding effect caused by the nitro substituent, although these aromatic signals could not be resolved.

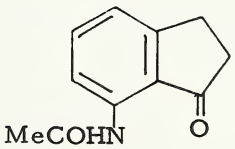
Acetylation of the amino-ester 127 by acetyl chloride gave the acetamido derivative, methyl 3-acetamidohydrocinnamate (128) quantitatively. The hydrolysis of the ester 128 was effected in 15% sodium hydroxide solution, while the amide function of the molecule remained intact. Although the synthetic route was more elaborate because of the esterification and subsequent hydrolysis, the procedure provided 3-acetamidohydrocinnamic acid (129) in a better yield. The IR spectrum of the acid indicated the disappearance of the ester carbonyl stretching and its replacement by an acid carbonyl stretching at 1720 cm^{-1}.

Cyclization of the acid 129 may lead to two isomeric products depending on the site of ring closure. It is reasonable to expect 5- and 7-acetamido-1-indanone to be the cyclized products. Various cyclizing agents were tried. Use was first made of sulfuric acid as in the case of p-acetamidophenylbutyric acid (84). However, the product did not show any ketone function when tested with 2,4-DNP reagent. The IR spectrum of the product showed an amine salt stretching band at 2580 cm^{-1}, indicating that hydrolysis had occured. No further attempt was made to characterize this amine salt. Polyphosphoric acid was the second cyclizing agent employed. Reaction temperature and time were varied in order to achieve the product; however, these experiments were not successful. Anhydrous

aluminum chloride was finally employed. This agent failed to cyclize p-acetamidophenylbutyric acid (84). The acid 129 was next converted to the corresponding acyl chloride which, without isolation, was treated with anhydrous aluminum chloride in the manner of a Friedel-Crafts intramolecular acylation. Fractional crystallization of the product gave 5-acetamido-1-indanone (m.p. 167-168°) (130) and the 7-acetamido analog (131) (m.p. 105-110°) in a ratio of 4:1. The IR spectrum of the isomeric mixture displayed two ketone absorption bands at 1695 and 1675 cm^{-1}, whereas that of the pure 5-acetamido-analog had one band at 1695 cm^{-1}, and that of the 7-acetamido-analog one band at 1675 cm^{-1}. The PMR spectra of these two isomers provided evidence for the isomeric assignments. The PMR spectrum of the 5-isomer displayed two aromatic singlets at δ 7.57 and 7.93. The former signal which integrated for two protons was assigned to H_4 and H_6, and the signal at δ 7.93 to H_7. No coupling was observed



130



131

between these protons because their chemical shift differences were small. A different pattern was noted in the spectrum of the 7-acetamido isomer 131. The aromatic signal of this compound exhibited two doublets and a triplet as shown below.

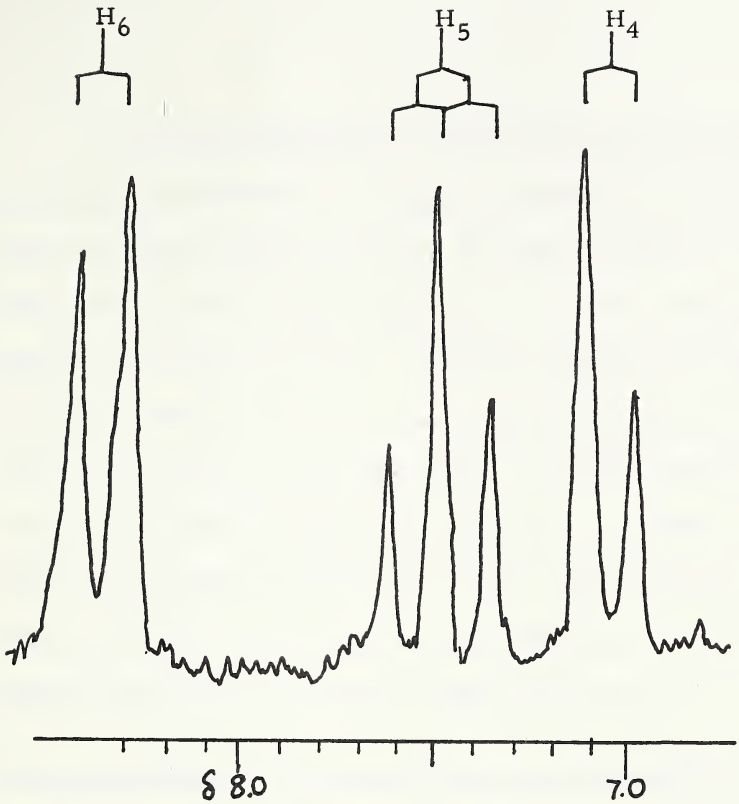


Figure 9 Part of PMR spectrum of 7-acetamido-1-indanone (131) recorded at 60 MHz in $CDCl_3$.

The triplet at $\delta 7.52$ is typical of the two ortho couplings of H_5. This coupling can only exist in compound 131 which has three adjacent protons, the middle of the three displaying two ortho couplings.

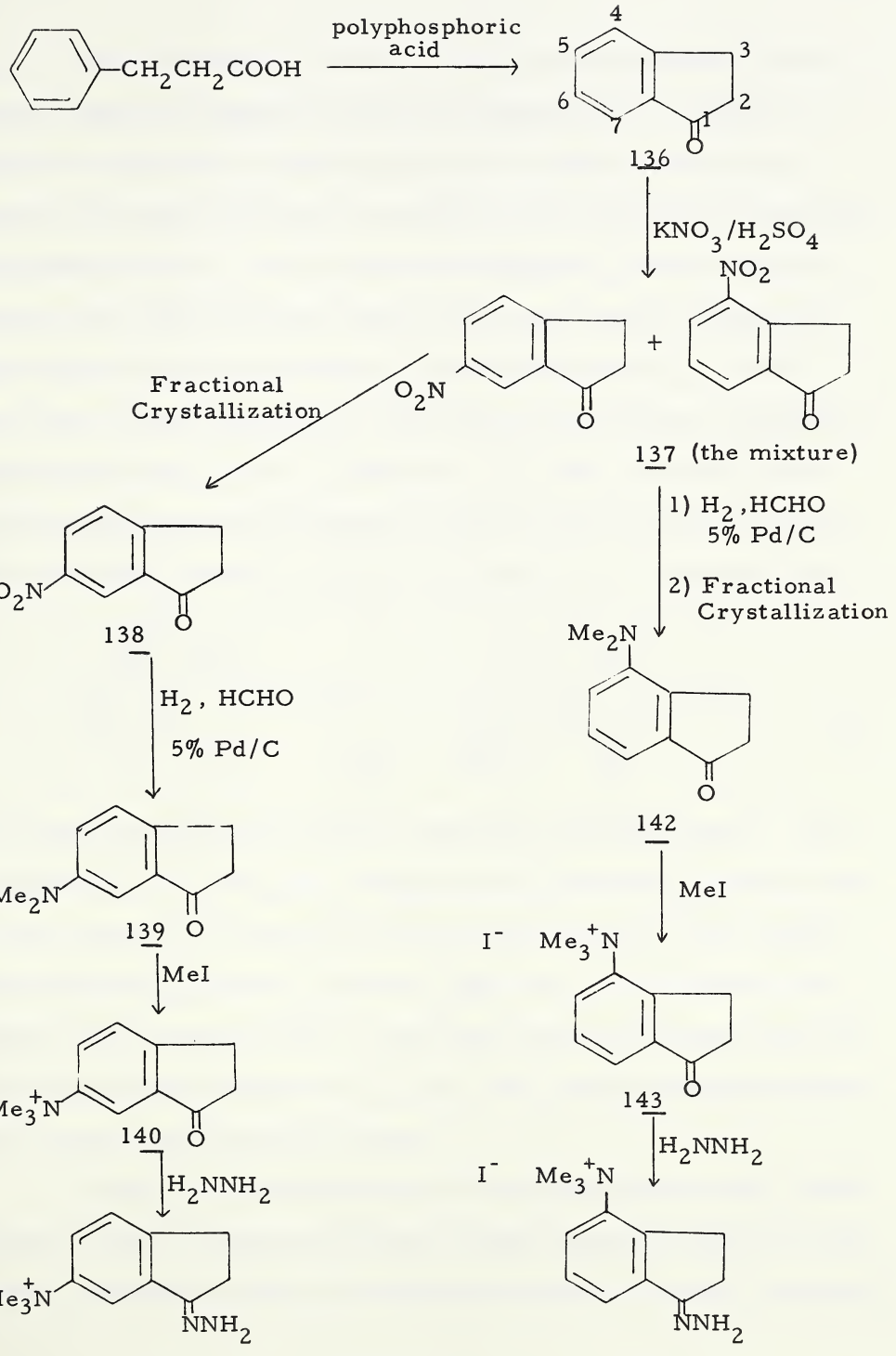
Acid hydrolysis of the amide 130 produced the corresponding primary amine 132. The IR spectrum of this compound displayed two absorption bands at 3455 and 3340 cm^{-1}, characteristic of a primary amine. The PMR spectrum clearly indicated that the shielding effect of the primary amine group was great enough to separate the H_6 and H_7 signals. Thus, an ortho coupling was noted for H_6 and H_7; the latter formed a doublet at $\delta 7.37$ (J = 8.7 Hz).

Reductive methylation of the amine 132 using formaldehyde, hydrogen and 5% Pd/C as catalyst yielded the tertiary amine 133, which was only characterized by its PMR spectrum. A singlet which integrated for six protons was noted at δ 3.05, the usual chemical shift for N-methyl protons. Treatment of the amine 133 with excess of methyl iodide formed the quaternary ammonium salt, 5-dimethylamino-1-indanone methiodide (134). A marked downfield shift was observed for the N-methyl protons of the methiodide salt 134; the nine proton singlet appeared at δ 3.90. The hydrazone 135 was prepared in the usual manner as described before and its IR spectrum showed NH stretching bands at 3350 and 3180 cm^{-1}.

4-Dimethylamino-1-indanone Hydrazone Methiodide (144) and 6-Dimethylamino-1-indanone Hydrazone Methiodide (141)

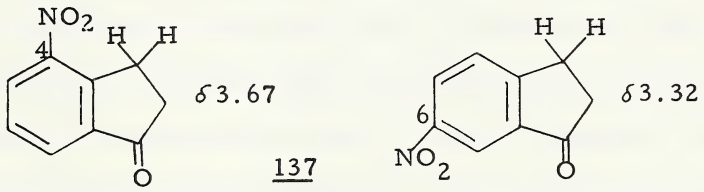
The compounds were prepared from the appropriately substituted nitro-1-indanones. The synthetic scheme for these two compounds is shown below (Scheme 17).

1-Indanone (136) may be prepared from hydrocinnamyl chloride in the manner of a Friedel-Crafts intramolecular acylation. Compound 136 may also be synthesized from a reaction of hydrocinnamic acid and polyphosphoric acid as mentioned earlier. The latter procedure was adopted using the experimental conditions described by Koo (1953). Thus, a mixture of hydrocinnamic acid and polyphosphoric acid in a ratio of 1:5 was heated on an oil bath then treated with ice water to give 1-indanone in a yield of 74%.


polyphosphoric acid
136
KNO3/H2SO4
NO2
O2N
Fractional Crystallization
137 (the mixture)
1) H2, HCHO 5% Pd/C
2) Fractional Crystallization
138
H2, HCHO 5% Pd/C
Me2N
142
MeI
139
MeI
I-
Me3+N
143
H2NNH2
140
H2NNH2
NNH2
141
144

Scheme 17

The preparation of 6-nitro-1-indanone (138) and the 4-nitro-analog followed a method of Ingold and Piggott (1923). 4-Nitro-1-indanone could not be isolated as reported by these authors who identified the site of nitration by oxidizing the compounds to the known nitrophthalic acids. In the present investigation, it was considered perhaps that PMR technique might confirm the isomer assignment. Extraction of the nitrated indanone with hot hexanes (b.p. 67-70°) permitted isomer separation. The first few extractions contained a mixture of 4- and 6-nitro-1-indanone. The PMR spectrum of the fraction displayed two multiplets arising from the methylene protons adjacent to the aromatic ring, at δ 3.32 and 3.67. The intensities



137

of the two multiplets were equal, indicating a 50:50% mixture. The multiplet at δ 3.67 was then assigned as the methylene protons of the 4-nitro isomer on account of its lower field position. The residue contained mainly 6-nitro-1-indanone (138), m.p. 71-74° (Ingold and Piggott, 1923, reported 74°). The PMR spectrum exhibited only one methylene proton multiplet at δ 3.32. The aromatic signals of these two isomers were not well resolved.

It may be noted that nitration of 1-tetralone (Schroeter, 1930) formed 7-nitro-1-tetralone (79) and 5-nitro-1-tetralone (80) in a ratio of 93:7, whereas nitration of 1-indanone resulted in 6-nitro-1-indanone

(138) and the 4-nitro isomer in a ratio of 5:1. The greater proportion of the 4-nitro isomer in the nitration of 1-indanone may be ascribed to the reduced degree of steric hindrance offered by the methylene protons adjacent to the aromatic ring as compared with the steric demands of the α-methylene protons in tetralones. A Dreiding model of 1-indanone confirms this explanation. Although 4-nitro-1-indanone could not be isolated, it was anticipated that the isomer might be separated in the next synthetic stage as 4-dimethylamino-1-indanone (142), either in the form of the free base or its hydrochloride salt. The NMe_2 proton signals might also have different chemical shifts for 4-amino (142) and the corresponding 6-amino isomer (139). This difference could be used to monitor the isomeric separation. 6-Dimethylamino-1-indanone (139) was synthesized by reductive methylation of the isomerically pure 6-nitro-1-indanone, and its PMR spectrum showed one NMe_2 signal at δ 2.93. The PMR spectrum of a mixture of 4- and 6-dimethylamino-1-indanone prepared from the mixture of nitro compounds (137) afforded two NMe_2 signals at δ 2.85 and 2.93. Fractional crystallization of the mixture yielded more 6-dimethylamino compound (139), while the mother liquor became more enriched in the 4-dimethylamino compound (142). Finally, the pure 4-isomer (142) was separated and its PMR spectrum exhibited only one NMe_2 signal at δ 2.85.

A mixture of 4-dimethylamino-1-indanone (142) and excess methyl iodide in acetone was stirred at room temperature for 24 hr, the methiodide salt (143) was obtained in a yield of 31%. In contrast,

5-dimethylamino-1-tetralone methiodide (100) could not be formed even upon heating the tertiary amine 96 with methyl iodide at 120° in a pressure bottle for 5 hr. This was clearly due to steric hindrance of the α-methylene group as discussed before. 6-Dimethylamino-1-indanone methiodide was prepared in a similar manner as the 4-analog 144.

Both methiodides, 140 and 143 were heated with 85% hydrazine respectively to form the hydrazones 141 and 144. It was found a reflux period of 2-4 hr invariably gave back the starting material; an overnight reflux period was required in both cases. This observation further confirmed that hydrazone formation was facilitated by positioning the electron withdrawing group, e.g. trimethylamino, at position para to the ketone function on the aromatic ring. In the case of indanone compounds, the 5-position is the only site where trimethylamino group can assist hydrazone formation. The IR spectrum of the compound 141 showed two NH stretching bands at 3380 and 3170 cm^{-1}, and that of the compound 144 displayed two NH stretching bands at 3315 and 3180 cm^{-1}. The spectra of both compounds indicated a loss of the carbonyl stretching band.

PHARMACOLOGY

Methods

A. Cat Sciatic Nerve-Tibialis Muscle Preparation

Cats, of either sex, weighing 1.2-3.0 kg were used. Anesthesia was induced with thiopental sodium (20-30 mg/kg intravenously) and maintained with chloralose (20-60 mg/kg intravenously). The trachea was cannulated and artificial respiration was applied throughout the experiment. Pointed drill rods were driven through the distal head of the femur and the tibia so that the leg could be rigidly clamped. The tibialis anterior tendon was cut and attached to a Grass force-displacement transducer FT10C (force rate 0.5 kg/mm). Twitches of the muscle were elicited by single square wave impulses of 0.1-0.3 m sec duration at a supramaximal voltage and a frequency of 20 shocks/min. Blood pressure was recorded from a carotid artery by a Statham transducer P23Dd. Drugs were administered through the femoral vein. Parameters were displayed on a Hewlett Packard Physiograph 7702B. Dose response lines were obtained for each compound in at least 3 cats and the dose which caused 50% blockade of the muscle twitches (ED_{50}) and the duration of blockade (D_{50}) at an ED_{50} determined. Mechanism of action was determined by attempting to reverse the neuromuscular blockade with edrophonium chloride (0.5 mg/kg) intravenously.

B. Frog Rectus Abdominis Muscle Preparation

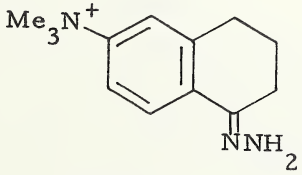
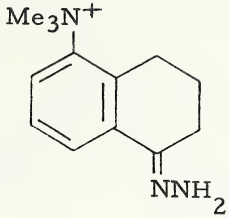
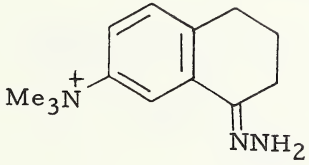
The frog rectus preparation was set up in a manner similar to that described for the determination of ACh agonist and antagonist

activity. ACh was used as a reference compound. For depolarizing blocking agents potency was compared to that of ACh, and for competitive blocking agents, gallamine triethiodide was used as a standard.

Results and Discussion

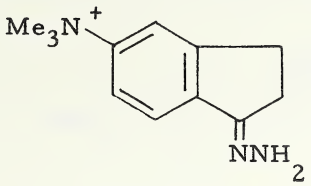
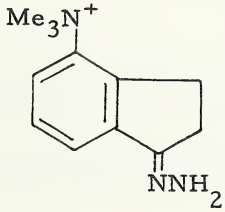
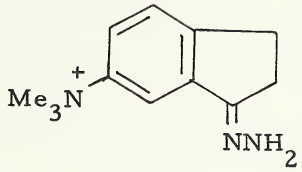
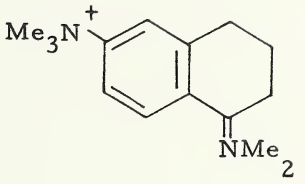
6-Dimethylamino-1-tetralone hydrazone methiodide (78), its 5-amino and 7-amino analogs (98 and 88), the corresponding 4-, 5-, and 6-dimethylamino-1-indanone hydrazone methiodide (144 , 135 and 141), and the N,N-dimethylhydrazones (106 and 107) were examined pharmacologically on the cat sciatic nerve-tibialis muscle preparation. The results have been summarized in Table 11 . The ED_{50} of 6-dimethylamino-1-tetralone hydrazone methiodide was found to be 1.6×10^{-4} mmol/kg, which was close to that of the literature value, 0.8×10^{-4} mmol/kg (Bamford et al., 1969), whereas the ED_{50} of the 5-amino and 7-amino analogs was greater than 1×10^{-2} mmol/kg. This result indicated that the relative position of the quaternary ammonium group and the hydrazone substitution was important in demonstrating neuromuscular blocking activity; the maximal potency was observed when the two substituents were in the para position on the aromatic ring. To establish that para-substitution was favored for the neuromuscular blocking activity in this class of compounds, the corresponding 4-, 5-, and 6-dimethylamino-1-indanone hydrazone methiodide (144, 135 and 131) were examined. It was interesting to note that the 5-amino isomer (135) (para-substituted) was ten times as active as the 6-amino isomer and more than twenty times as active as

Table 11 Neuromuscular Blocking Activities of Dimethylamino-1-tetralone Hydrazone Methiodides and Dimethylamino-1-Indanone Hydrazone Methiodides in the Cat[a]

Compounds	ED_{50} mmol/kg	D_{50} min[b]	Type of Neuromuscular Blockade
Suxamethonium	0.07×10^{-3}	5.0	depolarizing
 (78)	0.16×10^{-3}	5.2	depolarizing
 (98)	$>10 \times 10^{-3}$	---	---
 (88)	$>10 \times 10^{-3}$	---	---

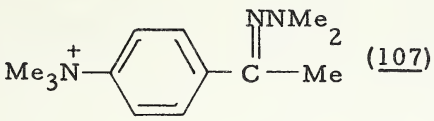
Continued ...

Table 11 - Continued

Compounds	ED_{50} mmol/kg	D_{50} min[b]	Type of Neuromuscular Blockade
 (135)	0.44×10^{-3}	10	depolarizing
 (144)	$>10 \times 10^{-3}$	---	---
 (141)	4.0×10^{-3}	17	depolarizing
 (106)	$>10 \times 10^{-3}$	---	---

Continued ...

Table 11 - Continued

Compounds	ED_{50} mmol/kg	D_{50} min[b]	Type of Neuromuscular Blocking
 (107)	5.8×10^{-3}	18	depolarizing

[a] Each figure represents the mean of three or more determinations.

[b] Duration of action in the cat.

the 4-amino analog. The distance between the two charged centres of tetralones and indanones are given below (Table 12). It can be noted that the optimal distance between the two nitrogen atoms is 7.9-8.1 Å (The configuration of the hydrazone substitution is believed to be anti-, which has been proven earlier). As mentioned before, potent neuromuscular blocking agents must possess a fully quaternized ammonium group and an electron negative feature capable of being protonated at the physiological pH. Therefore, it is not unreasonable for us to presume that the hydrazone group is protonated at physiological pH, and that this protonated group provides an additional "anchor" for the molecule in binding to the receptor. It is known that the degree of protonation of a base is parallel to its basicity. Consequently, the more basic the hydrazone the more active the compound will be as a neuromuscular blocking agent. In fact, it has been noted that 6-dimethylamino-1-tetralone methiodide (76) lacking a basic hydrazone substitution, is devoid of any activity. Similar results have been observed in neuromuscular blocking agents with androstane as nucleus (Bamford et al., 1971; 1967). The following table presents the relative molar potency among the androstane analogs.

Table 12 The Interonium Distance of the Tetralones and Indanones.

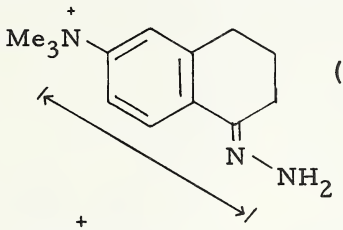
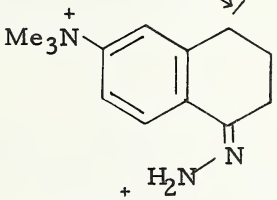
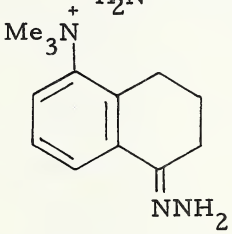
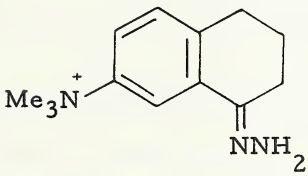
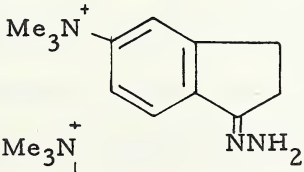
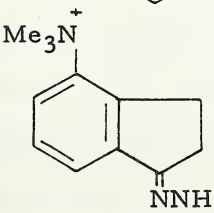
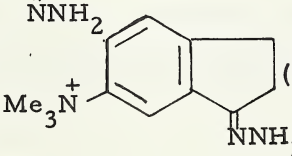
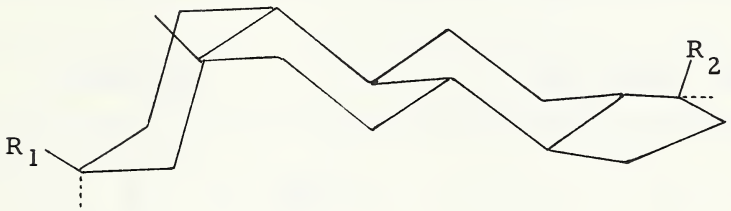
Compounds		Interonium Distance in Å
	(anti) (78)	7.9
	(syn)	6.2
	(98)	7.3
	(88)	6.4
	(135)	8.1
	(144)	7.4
	(141)	6.9

Table 13 The Relative Neuromuscular Blocking Activities of Some Androstanes (68,69) (Bamford et al., 1971)

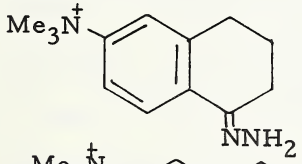
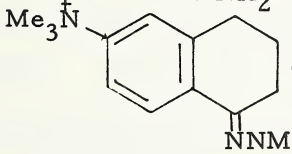
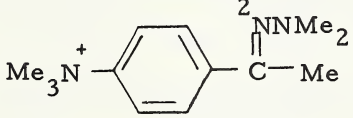
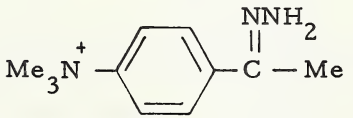


	R_1	R_2	Relative Molar Potency
a	$-N^+Me_3$	$-N^+Me_3$	1
b	$-N^+Me_3$	$-NMe_2$	1.07
c	$-N^+Me_3$	=O	0.025
d	$-N^+Me_3$	-OH	0.007

It can be noted that the analog (68b) with basic amino group is as active as the quaternary ammonium salt (68a). However, if the basic group is replaced by a ketone or hydroxyl function, the neuromuscular blocking activity is greatly reduced. Since a second basic group, which is capable of being protonated, was found to be favored for neuromuscular blocking activity, we decided to make and test more basic N,N-dimethylhydrazones 106 and 107. It was considered that if the potency of these compounds was parallel to the basicity of the hydrazones as expected, the N,N-dimethylhydrazones should be more

active than the plain hydrazone. The pK_a values of the hydrazones and the N,N-dimethylhydrazones were determined and are given below.

Table 14 pK_a Values of Some Hydrazone and N,N-Dimethylhydrazones*

Compounds	pK_a value	ED_{50} mmol/kg
 (78)	2.53	0.16×10^{-3}
 (106)	4.20	10×10^{-3}
 (107)	3.75	5.8×10^{-3}
 (145)	----	0.22×10^{-3}

*Each value represents the mean of three or more determinations.

It can be noted from the table that N,N-dimethylhydrazones 106 and 107 are more basic and have higher pK_a values than the hydrazone 78. In contrast to what we expected, they were found to be less active than the unsubstituted analog 78. Therefore, it seems that it is not the basicity of the hydrazone but some other factors that contribute to the neuromuscular blocking activity of this class of compounds. It may

be that the bulkiness of an N,N-dimethyl group opposes the binding of the charged hydrazone group to the appropriate site on the receptor, and thereby lowers the activity of these compounds. It has long been accepted that the optimal separation between the two nitrogen atoms in a fully extended suxamethonium or decamethonium molecule is 10 - 14 Å (Barlow and Ing, 1948; Paton and Zaimis, 1948). However, both suxamethonium and decamethonium are flexible molecules; the interonium distance could vary considerably. Thus, the use of freely flexible molecules in this type of study could be misleading, as has been pointed out by Alauddin and Martin-Smith (1965). The present study tends to support the two-point attachment hypothesis as proposed by (Bovet et al., 1949; Paton and Zaimis, 1949; Barlow and Ing, 1948). The optimal separation between the two charged centres, according to our finding, is approximately 7.9-8.1 Å.

The mechanism of action of these compounds was found to be depolarizing blockade, as the blockade was further intensified when edrophonium chloride, a cholinesterase inhibitor, was administered to the experimental animal as shown in Figure 10. It can be seen from the figure that neuromuscular blockade is intensified and the duration is prolonged by administration of edrophonium chloride. If these compounds were competitive blocking agents, the use of edrophonium chloride would have reversed the blockade and shortened the duration.

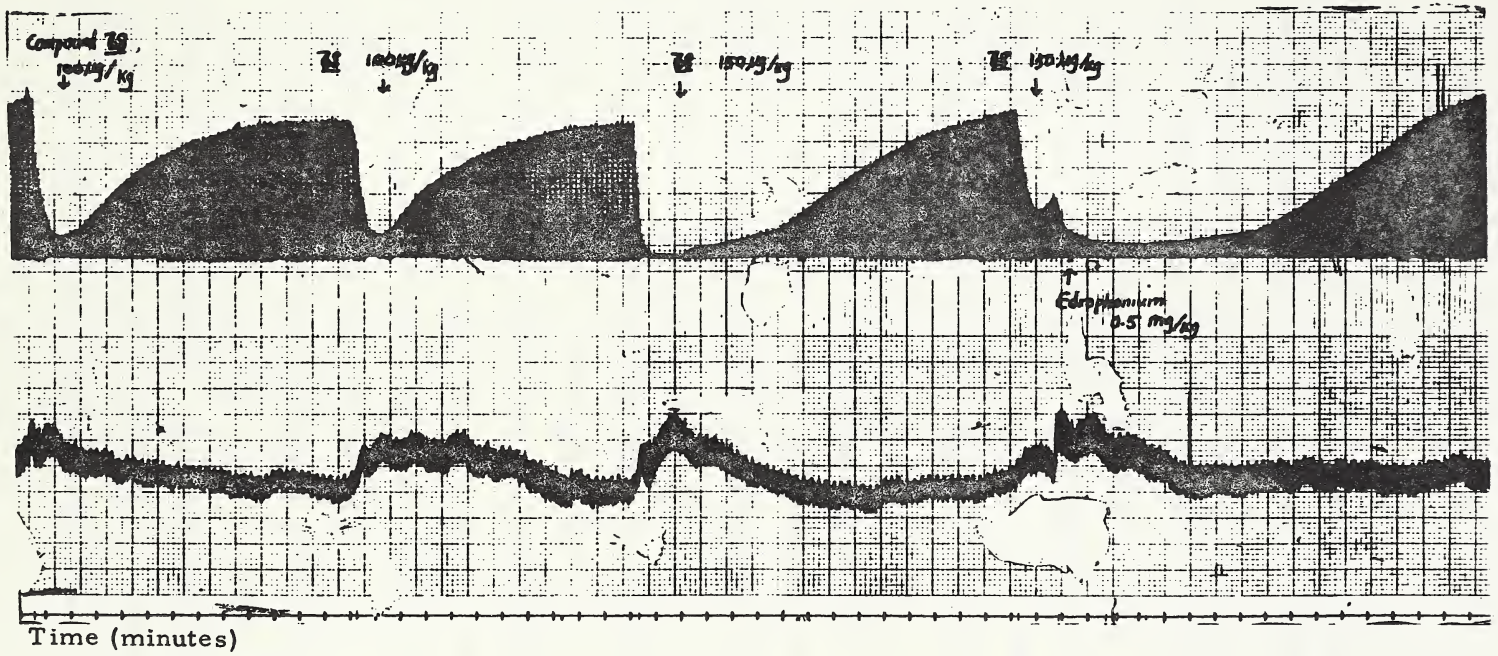
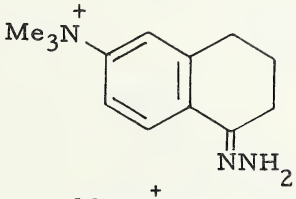
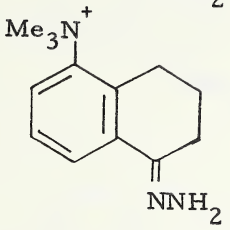
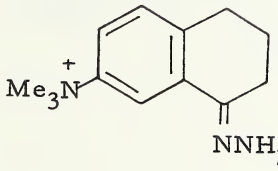


Figure 10 Attempts to Reverse Neuromuscular Blockade of Compound 78 with Edrophonium Chloride.

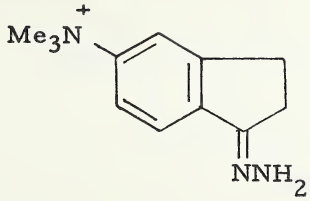
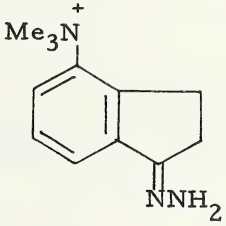
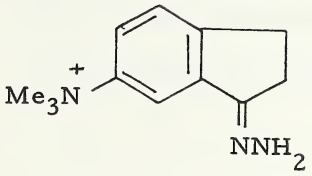
All these compounds were also evaluated pharmacologically on the frog rectus abdominis muscle. The results are summarized in Table 15. These compounds caused the frog rectus muscle to contract slowly. The depolarizing nature of these compounds is in agreement with the results on the cat preparation. Since these compounds induced muscle contraction, their activity was compared to that of ACh whose relative molar potency was set as 1000. It was of great interest to note that compounds 78 and 135, which were the most active members of the group of compounds tested on cats, were also the most active ones when tested on the frog rectus, their relative molar potency being 230 and 180. The only exception was found with 7-dimethylamino-1-tetralone hydrazone methiodide 88, it antagonized the effect of ACh on the frog rectus muscle, and was found to be 18 times more potent than gallamine triethiodide. It would be revealing of the structural requirements for this type of neuromuscular blocking agents if the hydrogenated analog, namely, 6-dimethylamino-1-decalone hydrazone methiodide (78) were successfully synthesized and tested. It is easily conceivable that different configurational isomers can be obtained in the fully hydrogenated compounds, and it would be of interest to compare neuromuscular blocking activity of the stereoisomers. Unfortunately, the synthesis of 121 encountered numerous difficulties and was not accomplished. However, the initial pharmacological results from the tetralones and indanone undoubtedly showed that further studies along this line would be rewarding.

Table 15 Acetylcholine Agonistic Activity and Antagonistic Activity of Dimethylamino-1-tetralone Hydrazone Methiodides and Dimethylamino-1-indanone Hydrazone Methiodides in the Frog.[a]

Compounds	Agonistic Activity Relative Molar Potency ACh = 1000	Antagonistic Activity Affinity Constant
Gallamine triethiodide	---	3.6×10^5
 (78)	230	---
 (98)	<2	---
 (88)	<2	6.4×10^4

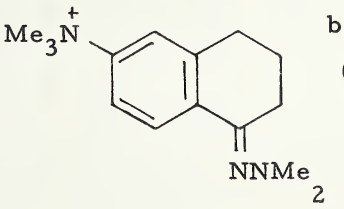
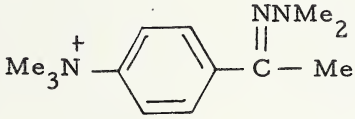
Continued ...

Table 15 - Continued

Compounds	Agonistic Activity Relative Molar Potency ACh = 1000	Antagonistic Activity Affinity Constant
 (135)	180	---
 (144)	<2	---
 (141)	27	---

Continued...

Table 15 - Continued

Compounds	Agonistic Activity Relative Molar Potency ACh = 1000	Antagonistic Activity Affinity Constant
 [b] (106)	<2	---
 (107)	14	---

[a] Each figure represents the mean of four or more determinations.

[b] Noncompetitive antagonist.

EXPERIMENTAL

SYNTHESIS OF DIMETHYLAMINOTETRALONE HYDRAZONE METHIODIDES, N,N-DIMETHYLHYDRAZONES, DECALONES AND THEIR INTERMEDIATES

6-Acetyltetralin (71)

The title compound was synthesized following a procedure of Schofield et al. (1949) with a slight modification. Anhydrous aluminum chloride was first introduced into the reaction flask; acetyl chloride was then added dropwise to the reaction mixture. This operation reversed the order of addition of anhydrous aluminum chloride and acetyl chloride, and was found to be practically convenient, yield 74%, b.p. 96-100°/0.07 mm (Schofield et al., 1949, reported 132.5-134.5°/3.5 mm, n_D^{20} 1.5572).

IR (film):

ν_{max} 1675 (C=O), 1605 (C=C) cm^{-1}.

PMR (CCl_4):

δ1.73 (4H, m, H_2 and H_3), 2.42 (3H, s, acyl Me), 2.73 (4H, m, H_1 and H_4), 7.05 (1H, d, J=8.5 Hz, H_8 aromatic), 7.57 (2H, m, H_5 and H_7 aromatic).

6-Acetyltetralin Oxime (72)

The title compound was prepared in an usual manner by heating the ketone 71 with hydroxylamine hydrochloride in the presence of pyridine as a base, yield 70%, m.p. 103-104° (from hexanes b.p. 67-70°). (Schofield et al., 1949, gave 105-106°).

IR (15% in chloroform):

ν_{max} 3590 (OH, free), 3250 (OH, H-bonded) cm^{-1}; a carbonyl stretching was absent.

PMR ($CDCl_3$):

δ1.88 (4H, m, H_2 and H_3), 2.30 (3H, s, acyl Me), 2.83 (4H, m, H_1 and H_4), 7.28 (3H, m, aromatic).

6-Acetamidotetralin (73)

The Beckmann rearrangement was investigated using different catalysts as follows.

i) Benzene sulfonyl chloride and pyridine method. (Gilmore and Horton, 1951). The oxime of 6-acetyltetralin (50 g, 0.26 mol) was dissolved in pyridine, and benzene sulfonyl chloride (60 ml) was added slowly to this solution through a separatory funnel. The reaction mixture was stirred vigorously, and the temperature kept below 15°. After 3 hr, the reaction mixture was poured onto ice (500 g) and diluted hydrochloric acid (200 ml). The precipitate was collected and recrystallized from ligroin (b.p. 100-115°) to give 20 g (40%) of the title compound, m.p. 105-106° (Gilmore and Horton, 1951, gave 106-107°).

ii) Acetic acid and hydrogen chloride method. (Schofield et al., 1949). The oxime 72 (22 g, 0.12 mol) was dissolved in a mixture of acetic acid (240 ml) and acetic anhydride (120 ml), and cooled externally in an ice bath. Hydrogen chloride was bubbled into the solution for a period of 2 hr. The reaction mixture was then allowed to stay at room temperature for 48 hr and poured onto

crushed ice (1000 g) with vigorous stirring. The precipitate was collected and recrystallized to give 19.8 g (90%) of the title compound, m.p. 98-101°.

IR (10% in chloroform):

ν_{max} 3450 (NH), 3310 (NH, H-bonded), 1683 (C=O), 1615 (C=C) cm^{-1}.

PMR ($CDCl_3$):

δ1.73 (4H, m, H_2 and H_3), 2.10 (3H, s, acyl Me), 2.68 (4H, m, H_1 and H_4), 7.12 (3H, m, aromatic), 7.98 (1H, br. s, NH).

6-Acetamido-1-tetralone (74)

To a solution of 6-acetamidotetralin (28.9 g, 0.15 mol) in acetic acid (70 ml) and acetic anhydride (20 ml) was added to a solution of chromium trioxide (20 g) in water (15 ml) and acetic acid (60 ml), while the solution was kept below 10° by external cooling. After stirring overnight, the solution was poured into ice water (1 l) and stirring was continued for another 2 hr. The product was collected, washed and recrystallized from ethyl acetate to give yellow crystals (14.5 g, 45%), m.p. 123-125° (Allinger and Jones, 1962, gave 124-125°).

IR (0.1% in chloroform):

ν_{max} 3445 and 3340 (NH), 1673 (C=O), 1605 (C=C) cm^{-1}.

PMR ($CDCl_3$):

δ2.20 (3H, s, acyl Me), 2.52 (6H, m, methylene), 7.68 (3H, m, aromatic protons well resolved, see the discussion).

6-Amino-1-tetralone (75)

6-Acetamido-1-tetralone (4.8 g, 0.024 mol) in 6N hydrochloric acid (30 ml) was heated under reflux for 3 hr. The reaction mixture was cooled and made basic; the liberated amine 75 was washed with water and dried (3.8 g, 98%). One recrystallization from aqueous ethanol gave crystals, m.p. 129-130° (Allinger and Jones, 1962, gave 129.5-130°).

IR (nujol mull):

ν_{max} 3405 and 3330 (NH), 3225 (H-bonded NH), 1648 (C=O) cm^{-1}.

PMR (DMSO-d_6):

δ2.36 (6H, m, methylene), 5.95 (2H, br. s, NH_2), 6.56 (2H, m, H_5 and H_7 aromatic), 7.62 (1H, d, J=8.5 Hz, H_8 aromatic).

6-Dimethylamino-1-tetralone Methiodide (76)

A mixture of 6-amino-1-tetralone 75 (2.9 g, 0.018 mol), methyl iodide (20 g) and anhydrous sodium carbonate (2.0 g) in water (30 ml) was heated under reflux for 48 hr. The solvent was evaporated in vacuo and the residue was recrystallized from ethanol and ether to give the title compound (3.6 g, 69%) as grey crystals, m.p. 147-148.5° (Bamford et al., 1969, gave 147-148°).

IR (nujol mull):

ν_{max} 1680 (C=O), 1605 (C=C) cm^{-1}; NH absorption bands were absent.

PMR (D_2O):

δ2.68 (6H, m, methylene), 3.83 (9H, s, $^{+}NMe_3$), 8.05 (3H,

m, aromatic).

6-Dimethylamino-1-tetralone Hydrazone Methiodide (78)

The title compound was prepared by boiling for 3 hr a solution of 6-dimethylamino-1-tetralone methiodide (1.65 g, 5 mmol) and 85% hydrazine (0.47 g, 8 mmol) in ethanol (25 ml). The solvent was removed and the residue recrystallized from ethanol and ether to yield greenish yellow crystals (1 g, 58%), m.p. 189-191° (Bamford et al., 1969, gave 189-191°).

IR (nujol mull):

$\tilde{\nu}_{max}$ 3350 and 3220 (NH), 1615 (NH, bending) cm^{-1}; C=O stretching absent.

PMR (DMSO-d_6):

δ2.36 (6H, m, methylene), 3.63 (9H, s, $^{+}NMe_3$), 6.61 (2H, br. s, NH_2), 7.85 (3H, m, aromatic).

3-(p-Acetamidobenzoyl)propionic Acid (82)

Premixed acetanilide (68 g, 0.5 mol) and succinic anhydride (58 g, 0.5 mol) were added to a suspension of anhydrous aluminum chloride (247 g) in carbon disulfide (300 ml), while the reaction mixture was cooled in an ice bath. The reaction mixture was stirred for $1\frac{1}{2}$ hr, and then allowed to stay at room temperature for two days. Decomposition of the mixture with ice water (2 l) yielded yellow precipitates which were taken up in a saturated sodium carbonate solution. This solution was filtered and made acidic with 10% hydrochloric acid to give the purified title compound (49 g, 45%),

m.p. 196-197° (Clapp and Krapcho, 1948, reported 202-205°).

IR (nujol mull):

ν_{max} 3340 (NH), 1710 (acid C=O), 1682 (ketone C=O), 1655 (amide C=O) cm^{-1}.

PMR (DMSO-d_6):

δ2.10 (3H, s, acyl Me), 2.60 and 3.20 (4H, m, methylene), 7.85 (4H, a pair of symmetric doublets aromatic), 10.22 (1H, s, COOH), 12.00 (1H, br. s, NH).

Methyl 4-(p-Acetamidophenyl)butyrate (83) and 4-p-Acetamidophenyl)-butyric Acid (84)

The acid 82 (4.7 g, 0.02 mol) in methanol (120 ml) was hydrogenated over 10% Pd/C (0.5 g) at room temperature and atmospheric pressure. When the calculated amount of hydrogen was taken up (ca 1.2 l), the catalyst was filtered off and the solution concentrated to give methyl 4-(p-acetamidophenyl)butyrate (83) as a colorless oil (4.0 g, 85%). IR spectrum of the oil displayed an ester carbonyl band at 1735 cm^{-1}, indicating an esterification accompanied the hydrogenation. The oil, without further purification, was heated with 15% sodium hydroxide solution (30 ml) on a steam bath for 15 minutes and poured into ice water. The solution was made acidic with 6N hydrochloric acid and the precipitate collected to give 4-(p-acetamidophenyl)butyric acid (84), m.p. 172-174° (from ethyl acetate and acetone, Bogdanov et al., 1961, reported 174-175°). The yield was 96%.

IR (nujol mull):

ν_{max} 3350 (NH), 1713 (acid C=O), 1630 (amide C=O) cm^{-1}.

PMR (DMSO-d_6):

δ2.04 (3H, s, acyl Me), 2.20 (6H, m, methylene), 7.34 (4H, a pair of doublets, aromatic), 8.17 (2H, br. s, COOH and NH).

4-(p-Acetamidophenyl)butyryl Chloride (85)

A mixture of the acid 84 (4.4 g, 0.02 mol), thionyl chloride (4.5 g, 0.04 mol) and anhydrous sodium carbonate (5 g) in benzene (20 ml) was stirred at room temperature for 4 hr. Excess sodium carbonate was filtered off, and the solvent removed. The residual oil was recrystallized from acetone and petroleum ether (30-60°) to yield the title compound (3.0 g, 63%), m.p. 90.5-93°.

IR (nujol mull):

ν_{max} 1780 (acyl chloride C=O), 1650 (amide C=O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.43; H, 5.55; N, 5.58.

7-Acetamido-1-tetralone (86)

i) Use of anhydrous aluminum chloride as catalyst.

Anhydrous aluminum chloride (3.0 g) was added portion-wise to a suspension of the acid chloride (85) (3.0 g, 0.02 mol) in carbon disulfide (20 ml), while the reaction mixture was cooled externally with ice. Stirring was continued for 6 hr and then the reaction mixture was poured into ice water (ca 300 ml) and extracted with chloroform. Evaporation of the solvent afforded a gummy mass

which did not give a positive test with 2,4-dinitrophenylhydrazine, a reagent for the identification of ketones. Reaction time was varied from 2 to 12 hr, but the title compound could not be formed. Reaction temperature was raised to 40° but this operation did not give a positive result either.

ii) Use of phosphorus oxychloride as catalyst.

A mixture of the acid 84 (1.05 g, 5 mmol) and phosphorus oxychloride (0.5 ml) in tetrachloroethane (20 ml) was heated for 2 hr. The solvent was removed and the residue decomposed by water and extracted with chloroform; the solvent was removed and yielded an oily residue which gave a negative test with 2,4-dinitrophenylhydrazine reagent.

iii) Use of sulfuric acid.

The acid 84 (8 g, 0.04 mol) was dissolved in sulfuric acid (60 ml), and heated in an oil bath at 80° for 16 hr. After cooling, the reaction mixture was poured into ice water (ca 500 ml) and 7-acetamido-1-tetralone was collected (4.5 g, 59%), m.p. 162-164° (von Braun, 1926, reported 165-166°). The product gave a positive test with the 2,4-dinitrophenylhydrazine reagent. Spectroscopic evidence also supported that the title compound was obtained.

IR (nujol mull):

ν_{max} 3360 (NH), 1690 (ketone C=O), 1675 (amide C=O) cm^{-1}.

PMR (DMSO-d_6):

δ2.07 (3H, s, acyl Me), 2.45 (6H, m, methylene), 7.42 (1H, d, J=8.5 Hz, H_5 aromatic), 7.86 (1H, a pair of doublets, J=2.0 Hz,

H_6 aromatic), 8.14 (1H, d, J=2 Hz, H_8 aromatic), 10.05 (1H, br. s, NH).

7-Amino-1-tetralone (81)

The title compound was synthesized by hydrolyzing the corresponding amide 86 in a manner similar to that described for the preparation of 6-amino-1-tetralone (75) in a yield of 97%, m.p. 135-137° (benzene) (von Braun, 1926, reported 137°).

IR (nujol mull):

ν_{max} 3440 and 3340 (NH), 1660 (ketone C=O) cm^{-1}.

PMR ($CDCl_3$):

The title compound resinified in the PMR solvent, no spectrum was obtained.

7-Dimethylamino-1-tetralone Methiodide (87)

A mixture of 7-amino-1-tetralone (2.8 g, 0.017 mol), methyl iodide 20 g, excess) and anhydrous sodium carbonate (2.0 g, 0.02 mol) in water (30 ml) was heated under reflux for 48 hr, and then additional amounts of anhydrous sodium carbonate (2.0 g, 0.02 mol) and methyl iodide (10 g) were added. The reflux was continued for another 24 hr, the solvent was removed, and the residue was recrystallized from methanol to give 4.0 g (71%) of the title compound, m.p. 203-204°.

IR (nujol mull):

ν_{max} 1690 (C=O) cm^{-1}; NH stretching bands were not observed.

PMR (DMSO-d_6):

δ2.58 (6H, m, methylene), 3.70 (9H, s, $^{+}NMe_3$), 7.97 (3H, m, aromatic).

Anal. Calcd. for $C_{13}H_{18}INO$: C, 47.15; H, 5.47; N, 4.23.
Found: C, 47.17; H, 5.55; N, 4.45.

7-Dimethylamino-1-tetralone Hydrazone Methiodide (88)

The title compound was prepared from compound 87 by the procedure described for the synthesis of the 6-analog 78. Yield was 72%, m.p. 160-162°.

IR (nujol mull):

ν_{max} 3390 and 3198 (NH), cm^{-1} absence of C=O stretching.

PMR (DMSO-d_6):

δ2.20 (6H, m, methylene), 3.61 (9H, s, NMe_3), 6.60 (2H, br. s, NH_2), 7.35 (1H, d, J=8.5 Hz, H_5 aromatic), 7.60 (1H, a pair of doublets, J=2.8 Hz, H_6 aromatic, 8.16 (1H, d, J=2.8 Hz, H_8 aromatic).

Anal. Calcd. for $C_{13}H_{20}IN_3$: C, 45.23; H, 5.84; N, 12.17.
Found: C, 45.70; H, 6.1; N, 12.22.

5-Nitrotetralin (90) and 6-Nitrotetralin (94)

The title compounds were prepared in a manner similar to that described by Schroeter (1922). Tetralin (132 g, 1.0 mol) was added dropwise to a cooled mixture of sulfuric acid (260 g) and 90% nitric acid (d=1.5) (120 g). The reaction mixture was kept at 0° during the addition of tetralin and this temperature was maintained

for 30 minutes after the completion of addition. Then carbon tetrachloride (300 ml) was added to extract the organic material. The organic layer was separated, washed with dilute sodium hydroxide solution and dried (calcium chloride). Removal of the solvent afforded an oil which was distilled in vacuo to give 137 g (76%) of a mixture of the title compounds, b.p. 160-170°/23 mm. The product was subjected to fractional distillation using a Vigreux column. The first fraction had a b.p. of 88-92°/0.06 mm (20 g), and was identified as the 5-nitro-isomer by its PMR spectrum. The second (92-94°/0.06 mm, ca 70 g) was a mixture of the 5- and 6-nitro isomer. The third (b.p. 94-98°/0.06 mm) was enriched in 6-nitrotetralin. PMR evidences to support the structural assignment are presented as follows.

5-Nitrotetralin

M.p. 32° (Schroeter, 1922, reported 34°).

PMR (CCl_4):

δ7.73 (4H, m, aromatic).

The PMR spectrum of this compound was found to be similar to that of 3-nitro-o-xylene, a compound which may be considered as an open chain analog of the 5-nitro compound. Thus, the aromatic signals of these two compounds are expected to be similar. The details are given in the discussion (p. 117).

6-Nitrotetralin

b.p. 94-98°/0.06 mm (Schroeter, 1922, gave 169°/13 mm).

PMR (CCl_4):

δ7.47 (4H, m, aromatic). The PMR spectra of the title compound and 4-nitro-o-xylene are similar in the aromatic region, and shown in the discussion (p. 115).

5-Nitro-1-tetralone (80) and 8-Nitro-1-tetralone (95)

5-Nitrotetralin (containing a small amount of the 6-nitro isomer) (100 g, 0.6 mol) was dissolved in glacial acetic acid (400 ml) and warmed to 70-80° on a steam bath. To this mixture was added with stirring a solution of chromic anhydride (80 g, 0.8 mol) in water (80 ml) in a period of 3/4 hr. The reaction mixture was kept at the same temperature for another 2 hr. Excess chromic anhydride was decomposed with methanol (10 ml). The solvent was removed and residue taken up in ether (300 ml). The ether solution was washed successively with water, 5% sodium bicarbonate and then water. Removal of the ether afforded the isomeric mixture (9.5 g, 8.4%) which was recrystallized from ligroin (b.p. 70-130°) to give 5-nitro-1-tetralone (2.3 g), m.p. 98-102° (Nakamura, 1940, reported 103-104°). The mother liquor was concentrated but further recrystallizations failed to separate the 8-nitro-isomer. Separation of the isomers was achieved with column chromatography. Alumina (500 g, Alcoa) was heated at 120° for 6 hr then cooled, and was deactivated partially with water (15 ml). The adsorbant was added portion-wise to a column (20 in x $1\frac{1}{2}$ in) previously filled with petroleum ether (b.p. 30-60°). The column was then loaded with

the residue obtained after evaporation of the mother liquor, and eluted with petroleum ether (b.p. 30-60°) with increasing chloroform content. When the chloroform content reached 25%, three components came out in the following order:

1st fraction, 5-nitro-1-tetralone (0.5 g).

2nd fraction, 6-nitro-1-tetralone (0.1 g), m.p. 102-104°, (Nakamura, 1940, reported 105°).

3rd fraction, 8-nitro-1-tetralone (1.0 g), m.p. 147-150°, (Nakamura, 1940, reported 153-154°)

i 7-nitro-1-tetralone (m.p. 104-105°) and the second fraction (6-nitro-1-tetralone) had a mixed m.p. of 74-85°.

ii The first and second fraction had a mixed m.p. of 65-80°.

PMR ($CDCl_3$):

i 5-Nitro-1-tetralone

δ7.39 (1H, t, J=8 Hz, H_7 aromatic), 8.00 (1H, a pair of doublets, J=1.5 Hz, H_8 aromatic), 8.25 (1H, a pair of doublets, J=1.5 Hz, H_6 aromatic).

ii 6-Nitro-1-tetralone

Three aromatic protons appeared as a singlet at δ8.06, indicating the extent of deshielding effect of the carbonyl and the nitro group were the same.

iii 8-Nitro-1-tetralone

The aromatic protons displayed an irresolvable multiplet at δ7.33.

5-Amino-1-tetralone (99)

Hydrochloric acid (10 ml) was added dropwise to a solution of 5-nitro-1-tetralone (2.0 g, 0.01 mol), stannous chloride (1.0 g) and ferrous sulfate (0.4 g) in methanol (10 ml); the rate of addition was so adjusted as to keep the reaction mixture gently refluxing. The reaction mixture was made basic with 20% sodium hydroxide solution, and extracted with ether (3 x 20 ml). Removal of the solvent afforded the title compound as a yellow residue (1.3 g, 77%). Recrystallization of the crude product from petroleum ether (b.p. 30-60°) gave yellow crystals with a m.p. 119-120° (Nakamura, 1940, reported 119-120°).

IR (nujol mull):

ν_{max} 3410 and 3340 (NH), 1665 (C=O) cm^{-1}; absence of NO_2 stretchings.

PMR ($CDCl_3$):

δ2.05 and 2.58 (6H, m, methylene), 3.62 (2H, br. s, NH_2), 6.67 (1H, a pair of doublets, J=1.5, H_6 aromatic), 7.03 (1H, t, J=8 Hz, H_7 aromatic), 7.43 (1H, a pair of doublets, J=1.5 Hz, H_8 aromatic).

Methylation of 5-Amino-1-tetralone (99)

i) Use of methyl iodide as methylating agent.

A mixture of the amine 99 (1.0 g, 0.006 mol), methyl iodide (3 g) and sodium carbonate (0.3 g) in water (5 ml) was heated under reflux for 48 hr. The mixture which was worked up as described for the

6-amino analog 76 , gave a dark gummy mass. Recrystallization of the mass from different solvents did not yield a solid compound which could be identified. Extraction of the mass with dilute hydrochloric acid followed by alkalininzation failed to recover the starting material. An attempt was made to replace water by ethanol as solvent, however, it too failed to give the desired product.

ii) Use of dimethyl sulfate as methylating agent.

A mixture of the amine 99 (0.75 g, 5 mmol), dimethyl sulfate (2 g, 0.016 mol), and 5% aqueous sodium hydroxide (5 ml) in ethanol (15 ml) was heated under reflux for 2 hr. The solvent was removed and the residue appeared as a dark oil. Recrystallization of the oil plus treatment with the active charcoal failed to give a solid compound for identification.

iii) Leuckart reaction.

The amine 99 (320 mg, 2 mmol) was heated with formaldehyde (33%, 1 ml) and formic acid (0.9 g) in water (4 ml). The reaction mixture became dark as heating continued. Working up the reaction mixture in the usual manner for the Leuckart reaction did not give the desired product, and a brown gummy mass was obtained.

iv) Use of methyl iodide and 2,6-lutidine as catalyst.

A method reported by Sommer and Jackson (1970) was employed in methylating the amine 99 , but was not successful. A solution of the amine 99 , (320 mg, 0.002 mol), methyl iodide (3 g) and 2,6-lutidine (428 mg, 0.004 mol) in acetone (5 ml) was stirred at room temperature for 12 hr and the precipitate was collected. The

IR spectrum (nujol mull) of the precipitate gave no carbonyl stretching band, and hence it was not the desired product. Evaporation of the solvent afforded an oil (90 mg). PMR spectrum (DMSO-d_6) of the oil displayed an NMe_2 signal at δ2.72. The IR spectrum of the residue displayed a carbonyl stretching band at 1693 cm^{-1}. These data indicated that some tertiary amine 96 formed.

5-Dimethylamino-1-tetralone (96)

A solution of 5-nitro-1-tetralone (2.1 g, 0.011 mol) and formaldehyde (37%, 6 ml) in ethanol (50 ml) was hydrogenated over 10% Pd/C at room temperature and atmospheric pressure. When the calculated amount of hydrogen was taken up (ca 1.2 l), the catalyst was filtered off and the solvent removed. Recrystallization of the residue from petroleum ether (b.p. 30-60°) yielded 1.4 g (67%) of 5-dimethylamino-1-tetralone, m.p. 60-62°. No elemental analysis was performed due to a short supply of the compound. However, the title compound was characterized by its IR and PMR spectrum.

IR (nujol mull):

ν_{max} 1693 (C=O) cm^{-1}.

PMR ($CDCl_3$):

δ2.28 and 2.80 (6H, m, methylene), 2.72 (6H, s, NMe_2), 7.52 (3H, m, aromatic).

Attempted Synthesis of 5-Dimethylamino-1-tetralone Methiodide (100)

A solution of the tertiary amine 96 (0.7 g, 3.7 mmol) and methyl iodide (10 g) in acetone (10 ml) was heated in a pressure reaction flask at 120° for 5 hr. The reaction mixture was allowed to cool and the solvent removed. The residue upon standing solidified and had a m.p. 57-62°. This was found to be the unreacted 5-dimethylamino-1-tetralone.

5-Dimethylamino-1-tetralone Methyl Tosylate (97)

A solid mixture of 5-dimethylamino-1-tetralone 86 (0.5 g, 2.5 mmol) and methyl-p-toluene sulfonate (0.5 g, 2.5 mmol) was heated on a steam bath for 96 hr in a nitrogen atmosphere. The fused solid was recrystallized from ethanol to give the title compound as brown crystals (800 mg, 80%), m.p. 194-195°.

IR (nujol mull):

ν_{max} 1685 (C=O), 1170 (S=O) cm^{-1}.

PMR ($CDCl_3$):

δ2.30 (3H, s, PhMe), 3.88 (9H, s, NMe_3), 7.60 (7H, m, aromatic).

Anal. Calcd. for $C_{20}H_{25}NO_4S$: C, 63.98; H, 6.71; N, 3.73.
Found: C, 63.61; H, 6.36; N, 3.77.

5-Dimethylamino-1-tetralone Hydrazone Methyl Tosylate (98)

The title compound was prepared by the same procedure as described for the synthesis of the 6-amino analog 78 in a yield of 48%, m.p. 140-142° (from ethanol/ether).

IR (nujol mull):

ν_{max} 3395 and 3310 (NH), 1200 (S=O) cm^{-1}, absence of a carbonyl stretching.

PMR (DMSO-d_6):

δ2.28 (3H, s, PhMe), 3.67 (9H, s, $^{+}NMe_3$), 5.40 (2H, br. s, NH_2, disappeared after deuteration), 7.50 (7H, m, aromatic).

Anal. Calcd. for $C_{20}H_{27}N_3O_3S$: C, 61.67; H, 6.99; N, 10.79. Found: C, 61.49; H, 7.20; N, 10.50.

8-Amino-1-tetralone (101)

The title compound was prepared from 8-nitro-1-tetralone by a procedure similar to that described for the 5-amino analog 89 in a yield of 70%, m.p. 75-77° (from ethanol). (Nakamura, 1940, reported 75-77°).

Attempted Synthesis of 8-Dimethylamine-1-tetralone Methiodide (102)

The procedure, employed to prepare the 6-amino-analog 76, was applied to synthesize the title compound, but it was not successful. Because of the limited amount of the primary amine 101, no further attempts were made to prepare the title compound.

6-Dimethylamino-1-tetralone N,N-Dimethylhydrazone Methiodide (106)

i) A mixture of 6-dimethylamino-1-tetralone (1.6 g, 0.005 mol), unsym-N,N-dimethylhydrazine (0.3 g, 0.005 mol) in ethanol (30 ml) was stirred at room temperature for 24 hr. The solvent was removed and the residue recrystallized from ethanol to give 1.3 g

of product, m.p. 125-130°, the IR spectrum of which was identical to that of the starting material.

ii) The previous reaction was slightly modified. The reaction mixture was heated for a period of 2 hr. However, a dark colored decomposed mass was obtained.

iii) A mixture of 6-dimethylamino-1-tetralone methiodide (1.6 g, 0.005 mol), unsym-N,N-dimethylhydrazine (0.6 g, 0.01 mol) and glacial acetic acid (0.6 g, 0.01 mol) in ethanol was heated under reflux for 3 hr. The solvent was removed and the residue was recrystallized from ethanol and methanol to give 1.2 g (67%) of the title compound, m.p. 177-178°.

IR (nujol mull):

Absence of a carbonyl absorption band.

PMR(DMSO-d_6):

δ2.58 (6H, s, NMe_2), 3.71 (9H, s, NMe_3), 8.02 (3H, m, aromatic).

p-Dimethylaminoacetophenone N,N-Dimethylhydrazone Methiodide (107)

i) A mixture of p-dimethylaminoacetophenone (0.61 g, 2 mmol) and unsym-N,N-dimethylhydrazine (0.18 g, 3 mmol) in methanol (20 ml) was heated under reflux for 2 hr. The solvent was removed and the residue was recrystallized (methanol) to give a white solid (m.p. 214-217°). The IR spectrum of the solid showed no carbonyl absorption band. The PMR spectrum of the solid displayed a nine proton singlet at δ3.30 and two exchangeable protons signal at δ6.18.

The solid was identified as unsym-N,N-dimethylhydrazine methiodide 109.

Compound 109 was prepared by reacting unsym-N,N-dimethylhydrazine and methyl iodide in acetone. M.p. of 109 was 223-225° (Merck, 1968, 223-225°). Mixed m.p. of the two above mentioned methiodides was 218-223°.

ii. When glacial acetic acid was used as described for the preparation of compound 107, the title compound was successfully synthesized in a yield of 80%, m.p. 168-169°.

IR (nujol mull):

Absence of a carbonyl absorption band.

PMR (DMSO-d_6):

δ2.47 (3H, s, CMe), 2.72 (6H, s, NMe_2), 3.83 (9H, s, $^+NMe_3$), 8.02 (4H, br. s, aromatic).

Anal. Calcd. for $C_{13}H_{22}IN$: C, 44.93; H, 6.39; N, 12.10.

Found: C, 44.66; H, 6.43; N, 11.98.

2,5-Dimethylphenylbutyric acid (112)

The preparation of 2,5-dimethylphenylbutyric acid followed a procedure of Kadyrov and Lainapov (1966). Anhydrous aluminum chloride (34 g, 0.26 mol) was added in portions into a mixture of n-butyrolactone (17.6 g, 0.2 mol) and p-xylene (21 g, 0.2 mol) while the reaction mixture was kept at 5° by external cooling. Then the reaction mixture was heated on a boiling water-bath for 15 minutes.

The cooled reaction mixture was poured into a mixture of ice (200 g) and hydrochloric acid (180 ml). The organic layer was extracted with benzene (3 x 150 ml), and the combined extracts were washed with water until the washings were neutral to congo red. Removal of the solvent afforded a colorless oil which was distilled to give the title compound (10 g, 26%), b.p. 160-162°/0.2 mm. (Kadyrov and Lainapov, 1966, gave 168-169°/0.7 mm).

IR (film):

ν_{max} 3400 and 2400 (OH, carboxylic acid), 1710 (C=O) cm^{-1}.

5,8-Dimethyl-1-tetralone (110)

A mixture of the acid 112 (10 g, 0.05 mol) and polyphosphoric acid (50 g) was heated with stirring in an oil bath at 110° for 15 minutes. The reaction mixture was poured immediately onto ice (400 g). The organic layer was extracted with ether (2 x 150 ml) and the extracts dried (Na_2SO_4). The solution was concentrated and the residue distilled in vacuo to give 8 g (88%) of 5,8-dimethyl-1-tetralone, b.p. 94-97°/0.1 mm. (Legros and Cagniant, 1961, reported m.p. 52°).

IR (film):

ν_{max} 1680 (ketone C=O) cm^{-1}; absence of OH stretching bands.

PMR ($CDCl_3$):

No exchangeable proton resonance signal when offset 200 Hz. δ2.30 (3H, s, C-5 Me), 2.62 (3H, s, C-8 Me), 7.47 (2H, m, aromatic).

Attempted Synthesis of 5,8-Dimethyl-1-tetralone N,N-Dimethyl-Hydrazone (111)

i) A mixture of 110 (1.7 g, 0.01 mol), acetic acid (0.8 g) and unsym-N,N-dimethylhydrazone (0.9 g, 0.015 mol) in ethanol was heated under reflux for $4\frac{1}{2}$ hr. The solvent was removed and the residue was examined by the IR spectroscopy. An absorption appeared at 1675 cm^{-1} indicating that unreacted starting material was recovered. Treatment of the residue with ethereal hydrogen chloride gave a solid (m.p. 76-78°) which was identified as unsym-N,N-dimethylhydrazine hydrochloride (Merck Index, 1968, gave m.p. 83°). Prolonged refluxing the reaction mixture up to a period of 24 hr did not afford the desired product.

ii) A mixture of 110 (1.7 g, 0.01 mol), unsym-N,N-dimethyl-hydrazine (1.8 g, 0.03 mol) and acetic acid (1.8 g) and xylene (20 ml) was placed in a thick-wall reaction flask and sealed. The reaction mixture was heated at 140° for 5 hr. The cooled reaction mixture was worked up as before. The residue gave an IR spectrum identical to that of the unreacted 5,8-dimethyl-1-tetralone.

Hydrogenation of 6-Acetamido-1-tetralone (74)

A mixture of 6-acetamido-1-tetralone (4.1 g, 0.02 mol) and ruthenium dioxide (200 mg) in absolute ethanol (50 ml) was stirred in an autoclave (0.5 l) at an initial hydrogen pressure of 1480 p.s.i.g. and 70-90°. The hydrogen-uptake stopped after 6-7 hr. The reaction mixture was treated with

off; the filtrate was concentrated to give an oil (4 g), which could not be solidified. The oil was soluble in 5% aqueous hydrochloric acid and therefore was probably an amino compound. The hydrochloride and hydrobromide salt of the reduced product were very hygroscopic, and could not be purified by recrystallization.

IR(1% free base in chloroform):

ν_{max} 3600 (OH), 3400-3000 (H-bonded NH_2 and OH) cm^{-1}.

6-Amino-1-decalol (113)

The title compound was synthesized from 6-amino-1-tetralone by a procedure similar to that described for the hydrogenation of 6-acetamido-1-tetralone in a yield of 92% (crude product). The hydrochloride and hydrobromide salt were very hygroscopic and could not be crystallized. Attempts to repeat the reduction on a large scale resulted in incomplete reduction (the PMR spectrum of the reduction product displayed aromatic signals). Therefore, the title compound was prepared by several small scale reactions.

IR (nujol mull):

ν_{max} 3500-3000 cm^{-1}, a broad band typical of primary amino-alcohol.

PMR (DMSO-d_6, 100 MHz):

δ2.72 (3H, br. s, NH_2 and OH, removed after deuteration), 2.57 (1H, br. s, H_6), 3.50 (1H, br. s, H_1), due to the presence of impurities the signal width dimensions could not be accurately measured.

Mass spectrum:

169 (9), 56 (100), 44 (28), 18 (33) m/e (% rel. abundance).

6-Acetamido-1-acetoxydecalin (116)

i) Acetyl chloride method.

Acetylchloride (1.5 g, 0.02 mol) was added with stirring to a cooled mixture of crude 113 (1.0 g, 0.006 mol) and triethylamine (2.0 g) in ethyl acetate (30 ml). The reaction mixture was heated under reflux for 2 hr, cooled and washed with water. The solution was dried (Na_2SO_4) and the solvent evaporated in vacuo to give the title compound as an oil (0.9 g). The oil could not be solidified.

ii) Acetic anhydride and pyridine method.

A mixture of crude 113 (2.0 g, 0.012 mol), acetic anhydride (20 ml) and pyridine (10 ml) was stirred at room temperature for 24 hr. Excess solvents were removed under reduced pressure; the residue was taken up in chloroform (20 ml), washed with water and dried (Na_2SO_4). Removal of the solvent afforded a residual oil which after one recrystallization from acetone and petroleum ether (b.p. 30-60°) gave the title compound (0.8 g, 27%), m.p. 122-127°. A second recrystallization raised the m.p. to 139-141°. This reaction was not reproducible everytime; sometimes oils did not solidify.

IR (nujol mull):

ν_{max} 3275 (NH), 1740 (C=O, ester), 1650 (C=O, amide), 1250 (COOR, ester) cm^{-1}.

PMR (DMSO-d_6):

δ3.65 (1H, br. s, H_6, $W\frac{1}{2}$ 20 Hz), 4.90 (1H, br. s, H_1, $W\frac{1}{2}$ 13.5 Hz), 7.68 (1H, d, $\underline{J}$=7 Hz, NH, removed after deuteration).

PMR (benzene-d_6, 100 MHz):

δ1.72 and 1.77 (6H, s, acyl Me), 3.88 (1H, br. s, $W\frac{1}{2}$ 20 Hz, collapsed to 16.5 Hz after deuteration, bw 28 Hz, H_6), 4.92 (1H, m, $W\frac{1}{2}$ 13.5 Hz, bw 20 Hz, H_1), 6.34 (1H, d, $\underline{J}$=7 Hz, NH, disappeared after deuteration).

Anal. Calcd. for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53.
Found: C, 66.61; H, 9.29; N, 5.51.

Attempted Synthesis of 6-Acetamido-1-decalol (117)

A mixture of 116 (7 g, 0.028 mol) and 15% aqueous sodium hydroxide (50 ml) was heated on a steam bath for 10 min. The cooled reaction mixture was extracted with ether (2 x 50 ml) and the combined extracts evaporated to give an oil (5.0 g). IR (film) of the oil displayed an amide C=O (1650 cm^{-1}) and an ester C=O (1740 cm^{-1} absorption band. The period of heating was prolonged (1 hr) and the reaction mixture was worked up as before. The oil was found to be soluble in 5% hydrochloric acid, an indication of partial hydrolysis of the amide functional group. The title compound could not be made from 116.

6-Benzamido-1-decalol (118)

A solution of benzoyl chloride (1.4 g, 0.01 mol) in benzene (10 ml) was added to 113 (1.67 g, 0.01 mol) in the same solvent

(20 ml). To this cooled mixture aqueous sodium hydroxide (10%, 5 ml) was added with vigorous stirring. The reaction mixture was stirred at room temperature for 5 hr. The precipitate and the benzene layer were combined and washed with 5% hydrochloric acid. Removal of the solvent afforded the crude title compound (1.7 g, 67%), m.p. 165-170°, which after one recrystallization (acetone and hexanes b.p. 66-68°) melted at 194-196°.

IR (nujol mull):

ν_{max} 1633 (C=O, amide) cm^{-1}.

PMR (DMSO-d_6):

δ4.37 (1H, d, J=5.5 Hz, OH, disappeared after deuteration). 3.50 (2H, br. s, H_1 and H_6 irresolvable).

PMR (pyridine-d_5, 100 MHz):

δ2.55 (1H, a pair of broad singlets, H_9), 3.87 (1H, br. s, H_6, $W\frac{1}{2}$ 22 Hz), 4.25 (H, br. s, H_1, $W\frac{1}{2}$ 26 Hz), 6.08 (1H, d, J=5.5 Hz, OH, disappeared after deuteration), 8.44 (1H, d, J=8 Hz, NH, removed after deuteration).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12.
Found: C, 74.84; H, 8.56; N, 5.21.

6-Benzamido-1-decalone (119)

A solution of the alcohol 118 (0.4 g, 0.0016 mol) in pyridine (3 ml) was added to an ice-cooled chromic anhydride-pyridine complex prepared by carefully dissolving chromic anhydride (0.4 g) in pyridine (9 ml). The reaction mixture was allowed to stay overnight and then diluted with water (50 ml). The diluted reaction mixture was extracted

with chloroform (3 x 20 ml), and the combined extracts evaporated to give 0.16 g (40%) of the title compound, m.p. 198-201° (from acetone and hexanes, b.p. 66-68°).

IR (nujol mull):

ν_{max} 3307 (NH), 1700 (C=O, ketone), 1633 (C=O, amide) cm^{-1}.

PMR ($CDCl_3$, 220 MHz):

δ3.93 (1H, m, bw 39 Hz, H_6), 6.13 (1H, d, J=7 Hz, NH).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16.

Found: C, 75.45; H, 8.13; N, 5.22.

Attempted Hydrolysis of 6-Benzamido-1-decalone (119)

i) Acid hydrolysis

The amide 119 (400 mg, 0.016 mol) was heated in a 50:50 mixture of conc. hydrochloric acid and glacial acetic acid for 8 hr. The glacial acetic acid was evaporated in vacuo and the residue was made basic with 20% aqueous sodium hydroxide, and extracted with chloroform (2 x 10 ml). Evaporation of the combined extracts afforded a residue (150 mg), m.p. 196-198°. IR (nujol mull) of the residue showed a strong C=O absorption band at 1633 cm^{-1}, indicating that the unhydrolyzable starting material was recovered.

ii) Base hydrolysis

A mixture of the amide 119 (100 mg, 4 mmol) and 5% ethanolic potassium hydroxide (10 ml) was heated under reflux for 24 hr. The solvent was removed, and the residue was extracted with ether (2 x 10 ml). Evaporation of the combined extracts yielded a residual

oil. The IR (nujol mull) of the oil displayed a strong amide C=O absorption band at 1635 cm^{-1} but a very weak ketone band at 1705 cm^{-1}.

Attempted Synthesis of 6-Dimethylamino-1-decalol (114) and 6-Dimethylamino-1-decalone (115)

Crude 113 (5.0 g, 0.03 mol) was dimethylated by a procedure similar to that described for 1-(N,N-dimethylaminomethyl)cyclohexanol (12a). The crude oil was distilled under reduced pressure (b.p. 116°/0.25 mm) to give 4.0 g (69%) of the title compound as a colorless liquid. The hydrochloride and hydrobromide salt of this compound were very hygroscopic and could not be purified. An analytic sample could not be obtained.

PMR (base in $CDCl_3$):

δ2.40 (6H, two singlets, NMe_2)

The dimethylated product was oxidized in a manner similar to that described for 118. IR (nujol mull) of the product exhibitied a very weak ketone band. PMR ($CDCl_3$) spectrum of the product showed no NMe_2 signal. The title compound could not be made by this procedure.

The oxidation of 114 with aluminum isopropoxide was also attempted. A mixture of 114 (1 g, 0.0016 mol), aluminum isopropoxide (3 g), dry acetone (50 ml) and dry benzene (100 ml) was heated under reflux in a nitrogen atmosphere for 12 hr. The solvents were removed and the residue extracted with 30% sulfuric acid (10 ml), and the extract was made alkaline with 20% aqueous sodium hydroxide. The basic solution was extracted with chloroform (2 x 20 ml) and the combined

extracts dried (Na_2SO_4) and evaporated. The IR spectrum of the product exhibited a strong absorption band at 3400 cm^{-1}, typical of OH group, whereas only a weak ketone band appeared at 1700 cm^{-1}.

cis,cis-1-Decalol (122)

The synthesis of cis, cis-1-decalol (122) followed a procedure of Meyers et al. (1964). 1-Naphthol was purified by recrystallization from benzene for this experiment. A solution of 1-naphthol (2 g, 0.013 mol) and acetic acid (0.5 ml) in ethanol (50 ml) was hydrogenated over 5% rhodium on alumina (1 g) at room temperature and at an initial hydrogen pressure of 60 p.s.i.g.. After the theoretical amount of hydrogen was absorbed, the catalyst was filtered off and the solvent removed. The residue was recrystallized from hexanes (67-70°) to give cis,cis-1-decalol (1 g), yield 47%, m.p. 93-95°. Meyer et al. (1964) reported a yield of 66%, m.p. 93-94°.

Attempted Reduction of 6-Acetamido-1-tetralone (74) using 5% Rhodium on Alumina

A mixture of 74 (1 g, 0.006 mol) and 5% Rh on alumina in absolute ethanol (40 ml) was shaken in a Parr hydrogenation apparatus at a hydrogen pressure of 68 p.s.i.g. for 24 hr, no hydrogen uptake was noted. The catalyst was filtered off and the filtrate concentrated to give an oil. The PMR ($CDCl_3$) spectrum of this oil displayed aromatic signals at δ7.27, showing that reduction failed.

Determination of pK_a values.

The pK_a values of 6-dimethylamino-1-tetralone hydrazone methiodide 78 , 6-dimethylamino-1-tetralone N,N-dimethylhydrazone methiodide 106 and p-dimethylamino acetophenone N,N-dimethyl-hydrazone methiodide 107 were determined using the method of Marshall (1955). An accurately weighed amount of base (ca 50 mg) was dissolved in freshly boiled distilled water (10 ml). To the solution was added a stoichiometric quantity of 0.1 N HCl. After mixing the pH of the solution was determined with a Beckmann pH meter (Zeromatic). The pK_a value of the compound was then calculated using the formula $pK_a = pH - \log [B]/[BH^+]$, where $[BH^+]$ is the concentration of the salt, namely, amount of 0.1 N HCl added, [B] is the concentration of the free base.

SYNTHESIS OF DIMETHYLAMINOINDANONES HYDRAZONE METHIODIDES AND THEIR INTERMEDIATES

m-Nitrocinnamic Acid (125)

A mixture of m-nitrobenzaldehyde (7.5 g, 0.05 mol), malonic acid (15 g, 0.15 mol), pyridine (31 ml) and piperidine (7.8 ml) was heated under reflux on a steam bath for 2 hr. The reaction mixture was cooled and poured into a mixture of hydrochloric acid (45 ml) and crushed ice (80 g). The precipitate (9 g, 98%) was collected, washed with water, and dried. Recrystallization from methanol gave the title compound, m.p. 198-200° (Heilbron, 1965, reported, 203-205°).

IR (nujol mull):

ν_{max} 1715 (C=O), 1620 (C=C), 1525 and 1357 (NO_2) cm^{-1}.

Methyl m-Nitrocinnamate (126)

A mixture of m-nitrocinnamic acid (5 g, 0.025 mol) and sulfuric acid (0.5 ml) in methanol (65 ml) was heated under reflux for 4 hr. The reaction mixture was cooled and placed in the refrigerator overnight. The title compound (5 g, 93%) precipitated, m.p. 124-125° (Heilbron, 1965, gave 123-124°). The compound was employed for the subsequent synthesis without further purification.

IR (nujol mull):

ν_{max} 1730 (C=O), 1620 (C=C), 1540 and 1340 (NO_2), 1260 (C-O) cm^{-1}.

PMR ($CDCl_3$):

δ3.83 (3H, s, OMe), 6.59 (1H, d, J=16 Hz, vinylic), 7.62 (5H, m, aromatic and vinylic).

Methyl m-Aminohydrocinnamate (127)

A solution of methyl m-nitrocinnamate (62 g, 0.3 mol) in ethyl acetate (1000 ml) was hydrogenated over 10% Pd/C (3.0 g) at room temperature and atmospheric pressure. After the theoretical amount of hydrogen was taken up (ca 27.0 l), the catalyst was filtered off, and the solvent removed in vacuo. The residual oil was distilled under reduced pressure to give the title compound (49 g, 91%), b.p. 116-118°/0.25 mm.

IR (film):

ν_{max} 3460 and 3380 (NH), 3230 (H-bonded NH), 1730 (C=O), 1260 (C-O) cm^{-1}.

PMR (CCl_4):

δ2.63 (4H, m, methylene), 3.55 (3H, s, OMe), 3.62 (2H, s, NH_2, disappeared after deuteration), 6.65 (4H, m, aromatic).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.14; H, 7.30; N, 8.09.

Methyl m-Acetamidohydrocinnamate (128)

Acetyl chloride (20.3 g, 0.26 mol) was added dropwise to a well stirred solution of methyl m-aminohydrocinnamate (47 g, 0.26 mol) and triethylamine (26 g, 0.26 mol) in benzene (700 ml). Triethylamine hydrochloride started to precipitate as soon as the acetyl

chloride was added. After the completion of addition, the reaction mixture was heated under reflux for 1 hr and then cooled. The precipitate was filtered off and the filtrate washed with water and dried (Na_2SO_4). Removal of the solvent gave the crude title compound (58 g, 100%), which was employed in the subsequent synthesis without purification. Recrystallizing a part of the product from acetone-hexanes gave m.p. 79.5-81°.

IR (nujol mull):

ν_{max} 3310 (NH), 1740, 1668 (C=O), 1260 (C-O) cm^{-1}.

PMR ($CDCl_3$):

δ2.13 (3H, s, acyl Me), 3.67 (3H, s, OMe), 7.25 (4H, m, aromatic), 8.87 (1H, br. s, NH, removed after D_2O exchange).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33.
Found: C, 65.05; H, 7.01; N, 6.00.

m-Acetamidohydrocinnamic Acid (129)

A mixture of methyl m-acetamidohydrocinnamate (21 g, 0.1 mol) and 15% aqueous NaOH (120 ml) was heated with vigorous stirring on a steam bath for 5-10 min until the solution became clear, then crushed ice was added immediately to stop the further hydrolysis of the amide group. The solution was then acidified with 20% HCl and the precipitate collected and recrystallized, m.p. 162° (from ethanol) (Heilbron, 1965, gave m.p. 162°).

IR (nujol mull):

ν_{max} 3350 (NH), 1720 and 1640 (C=O) cm^{-1}.

5-Acetamido-1-indanone (130) and 7-Acetamido-1-indanone (131)

m-Acetamidohydrocinnamic acid (16 g, 0.08 mol) and anhydrous sodium carbonate (8 g) were suspended in methylene chloride (240 ml). The reaction flask was cooled in an ice bath. To the mixture was added dropwise thionyl chloride (11.8 g, 0.1 mol) with vigorous stirring. Stirring was continued for 3 hr and the supernatant was collected by decantation. The solvent was removed and the residue was redissolved in another 200 ml of methylene chloride, and anhydrous aluminum chloride (16 g, 0.12 mol) was added. After another 4 hr period of stirring the reaction mixture was poured onto crushed ice (ca 400 g). The organic layer was taken up in chloroform (200 ml) and the chloroform extract dried (Na_2SO_4). Removal of the solvent gave the title compounds as an off-white solid (6 g, 36%). Fractional recrystallization from ethanol gave two fractions. The first fraction (2 g) had a m.p. of 167-168° and the second fraction (0.05 g), 105-110°.

IR (nujol mull, the mixture):

ν_{max} 1695 and 1675 (two ketone C=O), 1605 (amide C=O) cm^{-1}.

IR of the first fraction (5-acetamido-1-indanone):

ν_{max} 1695 (ketone C=O), 1605 (amide C=O) cm^{-1}.

PMR (DMSO-d_6) of 5-acetamido-1-indanone:

δ2.21 (3H, s, acyl Me), 7.75 and 7.93 (2H, two br. s, aromatic), 10.28 (1H, br. s, NH, disappeared after deuteration).

PMR (DMSO-d_6) of the second fraction (7-acetamido-1-indanone):

δ2.20 (3H, s, acyl Me), 7.08 (1H, d, J=8 Hz, H_4 aromatic),

7.62 (1H, t, J=8 Hz, H_5 aromatic), 7.83 (1H, d, J=8 Hz, H_6 aromatic), 10.4 (1H, br.s, NH).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40.

Found: (5-Acetamido-1-indanone) C, 70.26; H, 5.70; N, 7.40.

(7-Acetamido-1-indanone) C, 69.93; H, 5.62; N, 7.38.

5-Amino-1-indanone (132)

The title compound was preapred by a similar method to the one described for the synthesis of 6-amino-1-tetralone (75) in a yield of 70%, m.p. 184-186° (from ethanol).

IR (nujol mull):

ν_{max} 3455 and 3340 (NH), 3230 (NH, H-bonded), 1665 (C=O) cm^{-1}.

PMR (DMSO-d_6):

δ2.75 (4H, m, methylene), 6.15 (2H, br. s, NH_2), 6.62 (2H, m, aromatic), 7.73 (1H, d, J=8.7 Hz, H_7 aromatic).

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52.

Found: C, 73.69; H, 5.91; N, 9.46.

5-Dimethylamino-1-indanone Methiodide (134)

A solution of 5-amino-1-indanone (1.7 g, 0.012 mol) and 37% formaldehyde solution in methanol (50 ml) was hydrogenated at room temperature and atmospheric pressure, using 5% Pd/C (0.5 g) as catalyst. After the theoretical amount of hydrogen (ca 0.5 l) was taken up, the catalyst was filtered off and the solvent removed. The residue (133, 1.6 g) was dissolved in acetone (20 ml), and to the solution

excess of methyl iodide (10 ml) was added. The reaction mixture was stirred for 48 hr, and the title compound collected (1.5 g, 45%), m.p. 154-156° (from methanol-ethanol).

IR (nujol mull):

ν_{max} 1725 (C=O), 1610 (C=C) cm^{-1}.

PMR (D_2O):

δ2.90 and 3.40 (4H, m, methylene), 3.90 (9H, s, NMe_3), 8.18 (3H, m, aromatic).

Anal. Calcd. for $C_{12}H_{16}INO$: C, 45.44; H, 5.09; N, 4.42.
Found: C, 45.60; H, 5.09; N, 4.49.

5-Dimethylamino-1-indanone Hydrazone Methiodide (135)

The title compound was prepared from 5-dimethylamino-1-indanone methiodide in a manner similar to that described for 6-dimethylamino-1-tetralone hydrazone methiodide (78) in 67% yield, m.p. 164-166° (MeOH and H_2O).

IR (nujol mull):

ν_{max} 3350 and 3180 (NH) cm^{-1}; absence of a carbonyl stretching.

m-Aminohydrocinnamic Acid (136)

A solution of m-nitrocinnamic acid (6.0 g, 0.03 mol) in ethanol (600 ml) was hydrogenated over platinum oxide (0.3 g) at room temperature and pressure. When the calculated amount (ca 2.7 l) of hydrogen was taken up, the catalyst was filtered off and the solution concentrated. The residue (5.5 g) was recrystallized

from water to give 2.0 g (40%) of the title compound, m.p. 74-80° (Heilbron, 1965, gave 84-85°).

IR (nujol mull):

ν_{max} 2600 and 2340 ($^{+}NH_3$), 1715 (C=O) cm^{-1}.

m-Acetamidohydrocinnamic Acid (129)

To a solution of m-aminohydrocinnamic acid (4.0 g, 0.022 mol) and pyridine (1.8 g, 0.023 mol) in dioxane (120 ml) was added with vigorous stirring a solution of acetyl chloride (1.8 g, 0.023 mol) in the same solvent (20 ml). The reaction mixture was further heated under reflux for 2 hr. The solvent was removed, and the residue washed with water to give the title compound as a pale yellow solid (2.8 g, 39%), m.p. 147-150°. One recrystallization from aqueous ethanol raised the m.p. of the product to 157-160° (Heilbron, 1965, gave 162°).

1-Indanone (136)

A mixture of hydrocinnamic acid (10 g, 0.06 mol) and polyphosphoric acid (50 g) was heated, with vigorous stirring, in an oil bath at 110° for approximately 10 min. The color of the reaction mixture changed continuously during the course of heating, and served as an indication of the completeness of reaction. The reaction mixture was initially colorless, then turned to yellow, orange and finally to deep orange. Heating was stopped and the mixture was poured onto crushed ice (ca 300 g). The precipitate which formed was washed with water and dried. Vacuum distillation of the crude

product gave 6.3 g (74%) of the title compound as an oil which solidified forming colorless crystals, b.p. 94°/0.1 mm, m.p. 37-38° (Heilbron, 1965, gave m.p. 42°).

IR (nujol mull):

ν_{max} 1725 (C=O), 1610 (C=C) cm^{-1}.

PMR ($CDCl_3$):

δ2.63 and 3.05 (4H, m, methylene), 7.50 (4H, m, aromatic).

6-Nitro-1-indanone (138) and a Mixture of 6-Nitro and 4-Nitro-1-indanone (137)

The title compounds were prepared following a method of Ingold and Piggott (1923) in 74% yield (total isomers). 1-Indanone (12 g, 0.1 mol) was dissolved in sulfuric acid (150 ml) and cooled to 0-5°. To the mixture was added dropwise a solution of potassium nitrate (10 g) in sulfuric acid (30 ml). The reaction mixture was stirred in an ice bath for another $1\frac{1}{2}$ hr, then poured onto ice and the product collected, and fractionated by crystallization from hexanes (b.p. 67-70°). The separation of isomers was monitored by the PMR technique. The crude nitro-1-indanone mixture (12.5 g) was extracted with boiling hexanes, b.p. 67-70° (6 x 300 ml). The first and second extracts were combined, and found to be a 50:50 mixture of 4- and 6-nitro-1-indanone (6.0 g). The rest of the extracts were also combined and concentrated; this fraction contained mainly 6-nitro-1-indanone (6 g) and one more recrystallization of the fraction from the same solvent gave the pure 6-nitro isomer. The isomeric content of 6- and 4-nitro isomer was found to be 5:1, as shown by the

intensity of the methylene protons of the two isomers prior to fractionation.

IR (Total isomers, nujol mull):

ν_{max} 1720 (C=O), 1610 (C=C), 1525 and 1350 (NO_2) cm^{-1}.

6-Nitro-1-indanone (138)

m.p. 71-74° (Ingold and Piggott, 1923, reported 74°).

PMR ($CDCl_3$):

δ2.83 (2H, m, H_2), 3.32 (2H, m, H_3), 7.70 (3H, m, aromatic).

A mixture of 6- and 4-Nitro-1-indanone (137)

m.p. 74-77° (Ingold and Piggott, 1923, reported 77°).

PMR ($CDCl_3$):

δ2.83 (2H, m, H_2), 3.32 (2H, m, H_3 of the 6-nitro-isomer), 3.67 (2H, m, H_3 of the 4-nitro-isomer), 7.88 (3H, m, aromatic).

6-Dimethylamino-1-indanone (139)

The title compounds was prepared in a manner similar to that described for the synthesis of 5-dimethylamino-1-tetralone (96) in 85% yield, m.p. 78-80°.

IR (nujol mull):

ν_{max} 1695 (C=O), 1613 (C=C) cm^{-1}, and absence of the nitro stretching.

PMR ($CDCl_3$):

δ2.82 (4H, m, methylene), 2.93 (6H, s, NMe_2), 7.18 (3H, m, aromatic).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99.
Found: C, 75.73; H, 7.55; N, 8.02.

6-Dimethylamino-1-indanone Methiodide (140)

A solution of 6-dimethylamino-1-indanone (5.6 g, 0.03 mol) and methyl iodide (10 g, 0.07 mol) in acetone (100 ml) was stirred at room temperature for 24 hr. The bulk of acetone was removed and dry ether added until precipitation started; yield 60% (crude), m.p. 232-233° (methanol).

IR (nujol mull):

ν_{max} 1705 (C=O), 1610 (C=C) cm^{-1}.

PMR:

The title compound was practically insoluble in all NMR solvents and the spectrum could not be recorded. It was not further purified.

6-Dimethylamino-1-indanone Hydrazone Methiodide (141)

The title compound was synthesized by a similar procedure to that described for the preparation of 6-dimethylamino-1-tetralone hydrazone methiodide (78). However, the time of refluxing was 12 hr in order to form the hydrazone. Refluxing the ketone 140 with hydrazine for 2 or 4 hr invariably gave the starting material (IR evidence). The yield of hydrazone was 45%, m.p. 180-182° (methanol).

IR (nujol mull):

ν_{max} 3410 and 3315 (free NH), 3180 (NH, H-bonded) cm^{-1}; carbonyl stretching absent.

PMR (DMSO-d_6)

δ2.82 (4H, m, methylene), 3.70 (9H, s, NMe_3), 6.36 (2H, br. s, NH_2, disappeared after deuteration), 7.68 (3H, m, aromatic).

Anal. Calcd. for $C_{12}H_{18}IN_3$: C, 43.52; H, 5.48.

Found: C, 43.78; H, 5.33.

4-Dimethylamino-1-indanone (142)

A mixture of 4-nitro- and 6-nitro-1-indanone (8.0 g, 0.045 mol) was reductively methylated in a manner similar to the one described for the 6-nitro analog 138. Fractional crystallization from hexanes (b.p. 67-70°) and acetone gave 4.5 g (total amount) of 6-dimethylamino-1-indanone 139 as a major isomer. Evaporation of mother liquors afforded an oily residue (3.0 g), which was identified by PMR spectroscopy to be the title compound.

IR (film):

ν_{max} 1705 (C=O), 1605 (C=C) cm^{-1}.

PMR (Isomeric mixture, $CDCl_3$):

δ2.85 (4H, m, methylene), 2.85 (6H, s, NMe_2 of the 4-nitro-isomer), 2.93 (6H, s, NMe_2 of the 6-nitro-isomer), 7.18 (3H, m, aromatic).

PMR (4-dimethylamino-1-indanone, $CDCl_3$):

δ2.85 (6H, s, NMe_2), 2.88 (4H, m, methylene), 7.18 (3H, m, aromatic).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99.

Found: C, 75.97; H, 7.52; N, 7.82.

4-Dimethylamino-1-indanone Methiodide (143)

The title compound was synthesized by a similar procedure to the one described for the preparation of the 6-substituted analog 140 in 31% yield, m.p. 232-235° (from methanol). The compound was insoluble in PMR solvents, thus its spectrum could not be recorded.

IR (nujol mull):

ν_{max} 1700 (C=O), 1600 (C=C) cm^{-1}.

Anal. Calcd. for $C_{12}C_{16}INO$: C, 45.44; H, 5.09; N, 4.42.

Found: C, 45.16; H, 5.14; N, 4.18.

4-Dimethylamino-1-indanone Hydrazone Methiodide (144)

The title compound was prepared by the same method as that described for the 6-substituted analog 141 in a yield of 38%, m.p. 197-199° (from methanol).

IR (nujol mull):

ν_{max} 3380 (NH), 3170 (NH bond) cm^{-1}, absence of a carbonyl stretching.

PMR (D_2O – HCl):

δ2.93 and 3.73 (4H, m, methylene), 3.83 (9H, s, $^{+}NMe_3$), 7.92 (3H, m, aromatic).

Anal. Calcd. for $C_{12}H_{16}IN_3$: C, 43.52; H, 5.48; N, 12.69.

Found: C, 43.77; H, 5.08; N, 12.62.

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